



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/11, 15/63, 15/00, 15/12, A61K 38/17, C07K 16/00, C12P 21/02, C12Q 1/68, G01N 33/68		A1	(11) International Publication Number: WO 99/03990 (43) International Publication Date: 28 January 1999 (28.01.99)
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(22) International Filing Date: 15 July 1998 (15.07.98)		(72) Inventors; and	
(30) Priority Data: 60/052,661 16 July 1997 (16.07.97) US 60/052,872 16 July 1997 (16.07.97) US 60/052,871 16 July 1997 (16.07.97) US 60/052,874 16 July 1997 (16.07.97) US 60/052,873 16 July 1997 (16.07.97) US 60/052,870 16 July 1997 (16.07.97) US 60/052,875 16 July 1997 (16.07.97) US 60/053,440 22 July 1997 (22.07.97) US 60/053,441 22 July 1997 (22.07.97) US 60/053,442 22 July 1997 (22.07.97) US 60/055,726 18 August 1997 (18.08.97) US 60/055,724 18 August 1997 (18.08.97) US 60/056,359 18 August 1997 (18.08.97) US 60/055,725 18 August 1997 (18.08.97) US 60/055,985 18 August 1997 (18.08.97) US 60/055,952 18 August 1997 (18.08.97) US 60/055,946 18 August 1997 (18.08.97) US 60/055,683 18 August 1997 (18.08.97) US 60/055,989 18 August 1997 (18.08.97) US 60/056,361 18 August 1997 (18.08.97) US			
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		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
Published <i>With international search report.</i>			

(54) Title: 64 HUMAN SECRETED PROTEINS

(57) Abstract

The present invention relates to 64 novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.

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64 Human Secreted Proteins

Field of the Invention

This invention relates to newly identified polynucleotides and the polypeptides encoded by these polynucleotides, uses of such polynucleotides and polypeptides, and
5 their production.

Background of the Invention

Unlike bacterium, which exist as a single compartment surrounded by a membrane, human cells and other eucaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or
10 organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic reticulum
15 (ER). The ER separates the membrane-bounded proteins from all other types of proteins. Once localized to the ER, both groups of proteins can be further directed to another organelle called the Golgi apparatus. Here, the Golgi distributes the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes, and the other organelles.

20 Proteins targeted to the ER by a signal sequence can be released into the extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space - a process called exocytosis. Exocytosis can occur constitutively or after receipt of a triggering signal. In the latter case, the proteins are stored in secretory vesicles (or
25 secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane.

Despite the great progress made in recent years, only a small number of genes encoding human secreted proteins have been identified. These secreted proteins include
30 the commercially valuable human insulin, interferon, Factor VIII, human growth hormone, tissue plasminogen activator, and erythropoietin. Thus, in light of the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent medical disorders by using
35 secreted proteins or the genes that encode them.

Summary of the Invention

The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells, antibodies, 5 and recombinant methods for producing the polypeptides and polynucleotides. Also provided are diagnostic methods for detecting disorders related to the polypeptides, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying binding partners of the polypeptides.

10

Detailed Description

Definitions

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

In the present invention, "isolated" refers to material removed from its original 15 environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide.

20 In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce 25 a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid 30 sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having the translated 35 amino acid sequence generated from the polynucleotide as broadly defined.

In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig

analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard, 5 Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained 10 in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42° C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the 15 filters in 0.1x SSC at about 65°C.

Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages 20 of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37°C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH₂PO₄; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 µg/ml salmon sperm blocking DNA; followed by washes at 50°C with 1XSSPE, 0.1% SDS. In addition, to achieve even 25 lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include 30 Denhardt's reagent, BLOTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA+ sequences (such 35 as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a

complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

5 The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and 10 double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability 15 or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

20 The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, 25 as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. 30 Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, 35

formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins
5 such as arginylation, and ubiquitination. (See, for instance, PROTEINS -
STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W.
H. Freeman and Company, New York (1993); POSTTRANSLATIONAL
COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic
Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990);
10 Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

"SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y"
refers to a polypeptide sequence, both sequences identified by an integer specified in
Table 1.

"A polypeptide having biological activity" refers to polypeptides exhibiting
15 activity similar, but not necessarily identical to, an activity of a polypeptide of the
present invention, including mature forms, as measured in a particular biological assay,
with or without dose dependency. In the case where dose dependency does exist, it
need not be identical to that of the polypeptide, but rather substantially similar to the
dose-dependence in a given activity as compared to the polypeptide of the present
20 invention (i.e., the candidate polypeptide will exhibit greater activity or not more than
about 25-fold less and, preferably, not more than about tenfold less activity, and most
preferably, not more than about three-fold less activity relative to the polypeptide of the
present invention.)

25 **Polynucleotides and Polypeptides of the Invention**

FEATURES OF PROTEIN ENCODED BY GENE NO: 1

Preferred polypeptides encoded by this gene comprise the following amino acid
sequence:
30 IRHELGCSWRFRAVKAASAQGLFLSAPGPAARRCHGVVRCFSTCRALTA
RCTGRVPWEACLYSSEPLTETVARSVSWTCELALTCYAPRALSGAPVLCRHD
V (SEQ ID NO:155). Also provided are polynucleotides encoding such polypeptides.

This gene is expressed in human substantia nigra tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as
35 reagents for differential identification of the tissue(s) or cell type(s) present in a
biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, neurological disorders or abnormalities. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neurological systems, expression of this 5 gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain and of the tissue of the nervous system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue 10 or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:83 as residues: Pro-30 to Leu-35.

The tissue distribution indicates that the protein products of this gene are useful for diagnosis and treatment of neurological disorders and abnormalities. Many 15 polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:11 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the 20 present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 544 of SEQ ID NO:11, b is an integer of 15 to 558, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where the b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 2

This gene is expressed primarily in breast and testes.

Therefore, polynucleotides and polypeptides of the invention are useful as 30 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, tumors, particularly those of the breast or testes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the breast and testes, expression of this gene at significantly higher or lower levels may be routinely detected in certain 35 tissues or cell types (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., breast milk, seminal fluid, serum, plasma, urine, synovial fluid and

spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:84 as residues:

5 Ser-32 to His-37.

The tissue distribution indicates that the protein products of this gene are useful for diagnosis and treatment of disorders or abnormalities of breast and testes such as tumors of those tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences 10 are related to SEQ ID NO:12 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general 15 formula of a-b, where a is any integer between 1 to 701 of SEQ ID NO:12, b is an integer of 15 to 715, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 3

20 This gene is expressed in apoptotic T cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorder or abnormalities of T cells. Similarly, polypeptides and 25 antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissues of the immune system, developmental tissue, and 30 cancerous and wounded tissues) or bodily fluids (e.g., lymph seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in 35 SEQ ID NO:85 as residues: Met-1 to Glu-6, Leu-39 to Lys-46.

- The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of disorders in T cells and other immune system disorders such as inflammation. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:13 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 824 of SEQ ID NO:13, b is an integer of 15 to 838, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where the b is greater than or equal to a + 14.
- 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 4**
- The translation product of this gene shares sequence homology with ubiquitin-conjugating enzyme (UCE) involved in selective protein degradation. Based on the sequence similarity, the translation product of this gene is expected to share biological activities with UCE proteins. Such activities are known in the art and described elsewhere herein. Preferred polypeptides encoded by this gene comprise the following amino acid sequence:
- FLAIHFPTDFPLKPPKVAFTRMYFPNSNSNGSTCLDILWSQWSPAL (SEQ ID NO: 156). Also provided are polynucleotides encoding such polypeptides.
- This gene is expressed primarily in testes.
- 25 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders in testes, particularly cell cycle disorders, (e.g. testes tumor). Similarly, polypeptides and antibodies directed to these polypeptides are useful in
- 30 providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the testes and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissues, and cancerous and wounded tissues) or bodily fluids (e.g., seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene
- 35

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution and homology to ubiquitin-conjugating enzyme indicates that the protein product of this gene is useful for diagnosis and treatment of disorders
5 in testes and reproductive system such as tumors, as well as the treatment of tumors of other origins. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:14 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded
10 from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 499 of SEQ ID NO:14, b is an integer of 15 to 513, where both a and b correspond to the positions of nucleotide residues shown in
15 SEQ ID NO:14, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 5

This gene is expressed primarily in testes.

Therefore, polynucleotides and polypeptides of the invention are useful as
20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders and abnormalities in the testes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders
25 of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative
30 to the standard gene expression level, (i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder). Preferred epitopes include those comprising a sequence shown in SEQ ID NO:87 as residues: Ser-22 to Thr-32, Pro-37 to Ser-42.

The tissue distribution indicates that polynucleotides and polypeptides
35 corresponding to this gene are useful for diagnosis and treatment of disorders in testes and the reproductive system. Many polynucleotide sequences, such as EST sequences,

are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:15 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related 5 sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 698 of SEQ ID NO:15, b is an integer of 15 to 712, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where the b is greater than or equal to a + 14.

10

FEATURES OF PROTEIN ENCODED BY GENE NO: 6

This gene is expressed primarily in thymus, activated monocytes and spleen. Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a 15 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders and abnormalities of immune function and hematopoiesis, e.g. leukemia. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of 20 the immune and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endocrine tissue cell and tissue of the immune system, and haematopoietic tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having 25 such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that the protein products of this gene are useful for diagnosis and treatment of immunological and hematopoietic disorders such as leukemia. Many polynucleotide sequences, such as EST sequences, are publicly 30 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:16 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more 35 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 638 of SEQ ID NO:16, b is an integer of 15 to

652, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 7

- 5 This gene is expressed in T cells.
Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, T cell dysfunction. Similarly, polypeptides and antibodies directed to
10 these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded
15 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- The tissue distribution indicates that polynucleotides and polypeptides
20 corresponding to this gene are useful for diagnosis and treatment of disorders in T cells and immune systems. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically
25 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 728 of SEQ ID NO:17, b is an integer of 15 to 742, where both a and b correspond to the positions of nucleotide
30 residues shown in SEQ ID NO:17, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 8

- This gene is expressed primarily in pleural cancer and to a less extent in T cells.
Therefore, polynucleotides and polypeptides of the invention are useful as
35 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, pleural cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the pleural system, expression of this gene at 5 significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, pleural tissue and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in 10 healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:90 as residues: Ser-30 to Tyr-37.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of pleural cancer. 15 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. 20 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1205 of SEQ ID NO:18, b is an integer of 15 to 1219, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where the b is greater than or equal to a + 14.

25

FEATURES OF PROTEIN ENCODED BY GENE NO: 9

This gene is expressed in endothelial cells that shares the same origin as hematopoietic cells and in spleen and liver which are hematopoietic tissues.

Therefore, polynucleotides and polypeptides of the invention are useful as 30 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of endothelial cells or hematopoiesis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of 35 disorders of the above tissues or cells, particularly of the endothelial and hematopoietic systems, expression of this gene at significantly higher or lower levels may be routinely

- detected in certain tissues or cell types (e.g., endothelial tissue, haematopoietic cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of disorders in endothelial or hematopoietic systems. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:19 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 860 of SEQ ID NO:19, b is an integer of 15 to 874, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where the b is greater than or equal to a + 14.

20 FEATURES OF PROTEIN ENCODED BY GENE NO: 10

This gene is expressed primarily in breast lymph node and to a lesser extent in melanocytes.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metastatic melanoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the lymphatic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, cells and tissue of the immune system, cancerous and wounded tissues) or bodily fluids (e.g., lymph, breast milk, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution of this gene in melanocytes and lymph node indicates that the protein product of this gene is useful for the diagnosis and treatment of metastatic melanoma involving lymphatic tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of 5 these sequences are related to SEQ ID NO:20 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the 10 general formula of a-b, where a is any integer between 1 to 450 of SEQ ID NO:20, b is an integer of 15 to 464, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 11

15 This gene is believed to reside on chromosome 2. Therefore, this gene is useful in linkage analysis as a marker for chromosome 2.

This gene is expressed primarily in infant brain and to a lesser extent in fetal liver/spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as 20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above 25 tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural tissue, cells and tissue of the immune system, developing tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken 30 from an individual having such a disorder, relative to the standard gene expression level, (i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder). Preferred epitopes include those comprising a sequence shown in SEQ ID NO:93 as residues: Tyr-59 to Gln-68, His-84 to Leu-90, Ser-105 to Asn-110, Leu-112 to Pro-118.

35 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of neurological

disorders. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:21 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded

5 from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 623 of SEQ ID NO:21, b is an integer of 15 to 637, where both a and b correspond to the positions of nucleotide residues shown in

10 SEQ ID NO:21, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 12

This gene is expressed primarily in adipose tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as

15 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above

20 tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., adipose tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

25 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for regulation of fat metabolism and treatment of obesity. Many polynucleotide sequences, such as EST sequences, are publicly available

30 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:22 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more

35 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 738 of SEQ ID NO:22, b is an integer of 15 to

752, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:22, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 13

- 5 The translation product of this gene shares sequence homology with NADH:ubiquinone oxidoreductase, the first enzyme in the respiratory electron transport chain of mitochondria.
- 10 This gene is expressed primarily in HSC172 cells and to a lesser extent in pineal gland.
- 15 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, jet lag. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endocrine tissue, metabolic tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or
- 20 another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:95 as residues: Thr-30 to Val-38, Glu-49 to Ile-54.
- 25 The tissue distribution and homology to NADH:ubiquinone oxidoreductase indicates that polynucleotides and polypeptides corresponding to this gene are useful for minimizing the negative effects of travel across time zones by altering the body's circadian clock. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are
- 30 related to SEQ ID NO:23 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of
- 35 a-b, where a is any integer between 1 to 478 of SEQ ID NO:23, b is an integer of 15 to

492, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 14

- 5 This gene is expressed primarily in synovial IL-1/TNF stimulated cells. Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, arthritis. Similarly, polypeptides and antibodies directed to these 10 polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal tissue and cancerous and wounded tissues) or bodily fluids (e.g., 15 lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment of degenerative conditions of joints, including arthritis. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:24 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically 25 excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 518 of SEQ ID NO:24, b is an integer of 15 to 532, where both a and b correspond to the positions of nucleotide 30 residues shown in SEQ ID NO:24, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 15

- This gene is expressed primarily in 12 Week Old Early Stage Human. Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a 35 biological sample and for diagnosis of diseases and conditions which include, but are

not limited to, developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fetal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., developing tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of some developmental disorders. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:25 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 906 of SEQ ID NO:25, b is an integer of 15 to 920, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 16

This gene is expressed primarily in thymus and to a lesser extent in neutrophils. Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder,

relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of some immune disorders including lupus and other disorders involving thymic dysfunction. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:26 and may have been publicly available prior to conception of the present invention.
- Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 903 of SEQ ID NO:26, b is an integer of 15 to 917, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 17

This gene is expressed primarily in fibrosarcoma and to a lesser extent in IL1 and IPS induced neutrophils.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, fibrosarcoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., connective tissue, and cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:99 as residues: Gly-6 to Pro-11.
- The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of fibrosarcoma or

other immune disorders. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:27 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 648 of SEQ ID NO:27, b is an integer of 15 to 662, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 18

- Preferred polypeptides comprise the following amino acid sequence:
MLLTPHFNVANPQNLLAGLWLENEHSFTLMAPERARTHHCQPEERKVLFCLFP
15 IVPNSQAQVQPPQMPPFCCAAKEKTQEQLQEPLGSQCPDTCPNSLC (SEQ ID NO: 157). Polynucleotides encoding such polypeptides are also provided.

This gene is expressed primarily in jurkat T-Cells in S phase, and to a lesser extent in IL-1 and LPS induced neutrophils.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:100 as residues: Lys-97 to Gln-106, Gln-112 to Pro-118, Pro-123 to Lys-130, Arg-153 to Gly-158.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immune disorders related to jurkat T-cells and induced neutrophils. Many polynucleotide sequences, such

as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:28 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To 5 list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 685 of SEQ ID NO:28, b is an integer of 15 to 699, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where the b is greater 10 than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 19

The translation product of this gene shares sequence homology with FK506-binding protein FKBp-12 and FKBp13, members of a family of proteins which bind 15 the immunosuppressant drugs FK506 and rapamycin. The homology to FK506 binding proteins indicates that the protein encoded by this gene has similar activity to the known FK506 BP family members. Such activity may be assayed according to methods known in the art and described elsewhere herein. Preferred polypeptides encoded by this gene comprise the following amino acid sequence:

20 MRLFLWNAVLTLFVTSIGALIPEPEVK
IEVLQKPFICHRKTGGDMLVHYEGYLEKDGSLFHSTHKHNNGQPIWFTLGI
LEALKGWDQGLKGMCVGEKRKLIIPPAALGYGKEGKGKIPPESTLIFNIDLLEIR
NGPRSHESFQEMDLNDDWKLKDEVKAYLKKEFEKHGA VVNESHHDALVEDI
FDKEDEDKDGFISAREFTYKHDEL (SEQ ID NO: 158) or comprise a mature form
25 of the foregoing polypeptide having the following amino acid sequence:
EVKIEVLQKPFICHRKTGGDMLVHYEGYLEKDGSLFHSTHKHNNGQPIWF
TLGILEALKGWDQGLKGMCVGEKRKLIIPPAALGYGKEGKGKIPPESTLIFNIDL
LEIRNGPRSHESFQEMDLNDDWKLKDEVKAYLKKEFEKHGA VVNESHHDAL
VEDIFDKEDEDKDGFISAREFTYKHDEL (SEQ ID NO: 159). . Polynucleotides
30 encoding these polypeptides are also provided. Particularly preferred is the following
polynucleotide sequence:

ATGAGGCTTTCTTGTGGAACCGCGCTTGACTCTGTTCGTCACTTCT
TTGATTGGGGCTTGATCCCTGAACCAGAAGTAAAATTGAAGTTCTCCAGA
AGCCATTCACTGCCATCGCAAGACCAAAGGAGGGGATTGATGTTGGTCC
35 ACTATGAAGGCTACTTAGAAAAGGACGGCTCCTTATTCACTCCACTCACAA
ACATAACAATGGTCAGCCCATTGGTTACCTGGCATCCTGGAGGCTCTC

- AAAGGTTGGGACCAGGGCTTGAAAGGAATGTGTGTAGGAGAGAAGAGAAA
GCTCATCATTCCCTGCTCTGGCTATGGAAAAGAAGGAAAAGGTAAAATT
CCCCCAGAAAGTACACTGATATTAAATATTGATCTCCTGGAGATTGAAATG
GACCAAGATCCCATGAATCATTCCAAGAAATGGATCTTAATGATGACTGGAA
5 ACTCTCTAAAGATGAGGTAAAGCATATTAAAGAAGGAGTTGAAAAACAT
GGTCGGTGGTGAATGAAAGTCATCATGATGCTTGGTGGAGGATTTTT
GATAAAGAAGATGAAGACAAAGATGGTTTATATCTGCCAGAGAATTACAT
ATAAACACGATGAG TTA (SEQ ID NO:160), and the portion of it, nucleotide
residues 76 to the 3' end, which encode the mature form shown above.
- 10 This gene is expressed primarily in fetal heart, ovary, and thymus.
Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune dysfunction such as autoimmune disorders. Similarly,
- 15 polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and
- 20 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.
- 25 The tissue distribution and homology to FK506-binding protein FKBP-12 and FKBP13 indicates that polynucleotides and polypeptides corresponding to this gene are useful for identifying immunosuppressant drugs, and may be used in combination with immunosuppressant drugs for therapeutic purposes in the treatment of autoimmune diseases and organ/tissue transplant rejection. Many polynucleotide sequences, such as
- 30 EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the
- 35 present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1623 of

SEQ ID NO:29, b is an integer of 15 to 1637, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where the b is greater than or equal to a + 14.

5 **FEATURES OF PROTEIN ENCODED BY GENE NO: 20**

The protein product of this gene is believed to be the human homologue of yeast GAA1P which anchors proteins to cell surface membranes by glycosylphosphatidylinositol (GPIs). See, for example, Yeast Gaa1p is required for attachment of a completed GPI anchor onto proteins (J Cell Biol. 1995 May; 129(3): 10 629-639. PMID: 7730400; UI: 95247814).

This gene is expressed primarily in primary breast cancer and to a lesser extent in amniotic cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a 15 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the metabolic system, expression of this gene at 20 significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, amniotic cells and tissue and cancerous and wounded tissues) or bodily fluids (e.g., breast milk, lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., 25 the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:102 as residues: Pro-113 to Met-123.

The tissue distribution and similarity to GAA1P indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of 30 primary breast cancers. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:30 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is 35 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

formula of a-b, where a is any integer between 1 to 2128 of SEQ ID NO:30, b is an integer of 15 to 2142, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where the b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 21

This gene is expressed primarily in activated T-cells and to a lesser extent in prostate cancer and HSC172 cells.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune dysfunction and/or prostate cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and metabolic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, seminal fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:103 as residues: Ala-17 to Pro-26, Phe-92 to Tyr-97, Gly-104 to Glu-111.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of immune disorders and/or prostate cancer. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:31 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1550 of SEQ ID NO:31, b is an integer of 15 to 1564, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 22

This gene maps to chromosome 12, and therefore, may be used as a marker in linkage analysis for chromosome 12.

5 This gene is expressed primarily in breast tissues and to a lesser extent in fetal spleen.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast cancer, lactation deficiencies, and other breast related diseases, 10 including breast cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the haemolymphoid and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected 15 in certain tissues or cell types (e.g., breast tissue, cells and tissue of the immune system, and haemolymphoid tissue, cancerous and wounded tissues) or bodily fluids (e.g., lymph, breast milk, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or 20 bodily fluid from an individual not having the disorder.

The tissue distribution in tumors of breast origins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific 25 marker and/or immunotherapy target for the above listed tissues. Alternatively, The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are . useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include 30 bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors 35 of various blood lineages, and in the differentiation and/or proliferation of various cell types. Many polynucleotide sequences, such as EST sequences, are publicly available

and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:32 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

- 5 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1617 of SEQ ID NO:32, b is an integer of 15 to 1631, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where the b is greater than or equal to a + 14.

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FEATURES OF PROTEIN ENCODED BY GENE NO: 23

The translation product of this gene shares sequence homology with mutant or polymorphic BRCA1 gene which is thought to be important in the diagnosis and therapy of human breast and ovarian cancer as a predisposing gene (See Genebank

- 15 Accession No T17455). This gene maps to chromosome 18, and therefore, may be used as a marker in linkage analysis for chromosome 18.

This gene is expressed primarily in primary dendritic cells.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast, ovarian, and other reproductive related disorders and cancers. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the haemolymphoid and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, pleural tissue, breast tissue, and cancerous and wounded tissues) or bodily fluids (e.g., breast milk, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:105 as residues: Pro-13 to Lys-18, Ala-50 to Leu-58.

- 30 The homology to the mutant or polymorphic BRCA1 gene indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of breast and/or ovarian tumors, in addition to other tumors where

expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues. Alternatively, the tissue distribution within dendritic cells indicates that the protein product of this gene is useful for the detection/treatment of

5 neurodegenerative disease states and behavioral disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses , autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product

10 may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:33 and may have been publicly available prior to conception

15 of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 964 of SEQ ID NO:33, b is an

20 integer of 15 to 978, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 24

The translation product of this gene shares sequence homology with smaller hepatocellular oncoprotein which is thought to be important in protein synthesis (See Genebank Accession No. R07057).One embodiment of this gene comprises polypeptides of the following amino acid sequence: LRSVVQDHGQHGETPSLLKIQ @ (SEQ ID NO:161). An additional embodiment is the polynucleotides encoding these polypeptides.

30 This gene is expressed primarily in embryonic tissues and to a lesser extent in uterine cancer.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are 35 not limited to, hepatocellular tumors, and other disorders characterized by proliferating and/or developing tissues. Similarly, polypeptides and antibodies directed to these

polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the haemolymphoid system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:106 as residues: Asn-15 to Ser-20, Ile-32 to Asn-37.

The tissue distribution combine with the homology to a conserved human hepatocellular oncoprotein indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other proliferative disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Additionally, the expression also indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene may be useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy.

Alternatively, the homology to a hepatocellular protein indicates that the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:34 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or

more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 884 of SEQ ID NO:34, b is an integer of 15 to 898, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where the b is greater than or equal to a + 14.

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FEATURES OF PROTEIN ENCODED BY GENE NO: 25

- The translation product of this gene shares sequence homology with a gene encoding for anti-heparanase activity which is thought to be important in inhibition of heparin or heparan sulphate degradation. Moreover, this gene was shown to have
- 10 homology to the human 3-oxo-5-beta-steroid 4-dehydrogenase, which is known to be important in metabolism since it catalyzes the reduction of delta(4) double bonds of bile acid intermediates and steroid hormones carrying the delta(4)-3-one structure in the A/B Cis configuration (See Genebank Accession No. Z28339) One embodiment of this gene comprises polypeptides of the following amino acid sequence:
- 15 MFYNFVRQLDTVSIEHAGKSKLKMTVGTKLTSQXGPRKSSQSGRIAASITDCQ
QCKA @ (SEQ ID NO:162), and/or
MEAAAILPLWLLFLGPXPESVPTVIFNLDFPACSLTVSSCLTKL @ (SEQ ID
NO:163). An additional embodiment is the polynucleotides encoding these
polypeptides.
- 20 This gene is expressed primarily in fetal tissues.
Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, arthritis, metabolic disorders, as well as reproductive disorders.
- 25 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the haemolymphoid system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g. reproductive, metabolic,
- 30 cancerous and wounded tissues) or bodily fluids (e.g., bile acid, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.
- 35 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of cancer and other

proliferative disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Additionally, the expression indicates that this protein may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages.

5 In such an event, this gene may be useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus this protein may also be involved in apoptosis or tissue

10 differentiation and could again be useful in cancer therapy. Alternatively, based upon its homology to a conserved human anti-heparanase gene, mutations of which are known to be important in the predisposition of arthritis, may suggest that this protein may also be important in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism,

15 spinal deformation, and specific joint abnormalities as well as chondrodysplasias i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid. Moreover, the homology to a conserved human metabolic gene may suggest that the protein product of this gene is useful for the diagnosis, prevention, and/or treatment of various metabolic disorders

20 such as Tay-Sachs disease, phenylketonuria, galactosemia, porphyrias, and Hurler's syndrome. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:35 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded

25 from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 740 of SEQ ID NO:35, b is an integer of 15 to 754, where both a and b correspond to the positions of nucleotide residues shown in

30 SEQ ID NO:35, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 26

The translation product of this gene shares sequence homology with pulmonary hydrophobic surfactant-associated proteins which is thought to be important in useful

35 for normalising pulmonary surface tension (See Genebank Accession No. N80643).

This gene is expressed primarily in embryonic tissues.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hyaline membrane disease, developmental and pulmonary disorders.
- 5 Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the respiratory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., pulmonary tissue, developing
- 10 tissue and cancerous and wounded tissues) or bodily fluids (e.g., surfactant, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.
- 15 The tissue distribution and homology to pulmonary hydrophobic surfactant-associated proteins indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of such lung related diseases such as hyaline membrane disease which is often characteristic of premature infants - leading to significant pulmonary disorders throughout childhood. Alternatively, The tissue
- 20 distribution indicates that polynucleotides and polypeptides corresponding to this gene are . useful for the diagnosis and treatment of cancer and other proliferative disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Additionally, the expression indicates that this protein may play a role in the
- 25 proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, this gene may be useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern
- 30 formation. Thus this protein may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:36 and may have been publicly available prior to conception of the present invention. Preferably, such related
- 35 polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the

present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 685 of SEQ ID NO:36, b is an integer of 15 to 699, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 27

This gene is expressed primarily in fetal tissue and to a lesser extent in thymus. Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immunological disorders, particularly immunodeficiency. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the haemolymphoid system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, developing tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:109 as residues: Pro-18 to Trp-24.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in thymus indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have

- commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:37 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 957 of SEQ ID NO:37, b is an integer of 15 to 971, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:37, and where the b is greater than or equal to a + 14.
- 15 **FEATURES OF PROTEIN ENCODED BY GENE NO: 28**
- This gene is expressed primarily in small intestine and to a lesser extent in ulcerative colitis.
- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, ulcers, acid reflux and other gastrointestinal disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the digestive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., gastrointestinal tissue, and cancerous and wounded tissues) or bodily fluids (e.g., bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:110 as residues: Ile-2 to Ser-8, Gln-23 to Ser-31, Lys-61 to Lys-66, Lys-74 to Thr-79, Val-138 to Glu-160, Glu-178 to Thr-183.
- 35 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and diagnosis of digestive and

- gastrointestinal problems such as acid reflux or ulcers. Alternatively, the tissue distribution may suggest that the protein product of this gene is useful for the diagnosis, prevention, and/or treatment of various metabolic disorders such as Tay-Sachs disease, phenylketonuria, galactosemia, porphyrias, and Hurler's syndrome.
- 5 Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:38 and may have been publicly available prior to conception of the present invention. Preferably,
- 10 such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 858 of SEQ ID NO:38, b is an integer of 15 to 872, where both a and b
- 15 correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 29

- The translation product of this gene was shown to have homology to catalase
- 20 (See Genebank Accession No. pirlA55092IA55092) which is known to play an integral role in the oxidative prophylaxis in eukaryotic and mammalian cells. One embodiment of this gene comprises polypeptides of the following amino acid sequence:
- NHGHSCFLCEIVRSQFHTTYEPEA @ (SEQ ID NO:164), and/or
SGRHRVELQLLFPLVRVNFEGLGVNHGSCFLCEIVRSQFHTTYEPEA @ (SEQ
25 ID NO:165). An additional embodiment is the polynucleotides encoding these polypeptides. This gene maps to chromosome 3, and therefore, may be used as a marker in linkage analysis for chromosome 3.

This gene is expressed primarily in skin and to a lesser extent in human uterine cancer.

- 30 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, uterine cancer; fibrosis; melanoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes
- 35 for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the epidermis and/or reproductive system,

- expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., integumentary tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder,
- 5 relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution combined with the homology to catalase indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment and/or diagnosis of human uterine cancer and potentially, all cancers in general

10 (particularly of the epidermis) due to the fact that diminished catalase activity has been shown to lead to significant cellular damage which could predispose cancer. Likewise, this gene and/or its protein product may be useful in the treatment and/or diagnosis of other disorders of the skin, such as fibrosis or in wound healing. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or

15 immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To

20 list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 594 of SEQ ID NO:39, b is an integer of 15 to 608, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where the b is greater

25 than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 30

This gene is expressed primarily in fetal liver/spleen and bone marrow stromal cells, and to a lesser extent in neural tissues (brain; spinal cord) and cancers

30 (glioblastoma; chondrosarcoma).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancers, particularly of glial cells and cartilage; hematopoietic and other immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the

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- tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic/immune system and CNS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic cells and tissue, and cancerous and wounded tissues) or
- 5 bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:112 as residues: Arg-2 to Asp-7.
- 10 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the expansion, proliferation, and/or differentiation of hematopoietic cells. This gene is expressed predominantly at sites of hematopoiesis, such as fetal liver and bone marrow, and thus may control the proliferation and/or differentiation of hematopoietic stem and progenitor cells. Thus it
- 15 could be used for chemoprotection, or for the production of specific blood cell lineages, as well as the amplification of stem cells. Additionally, its expression in neural cells of the brain and spinal cord suggest that it may also play a role in the maintenance and differentiation of neuronal stem cells, or in the treatment of neurological disorders, such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome,
- 20 schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses , autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked
- 25 disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Finally, its observed expression in various cancers suggest that it may play a role in the control of cell proliferation. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through
- 30 sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a
- 35 nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 841 of SEQ ID NO:40, b is an integer of 15 to 855, where both a and b

correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 31

- 5 This gene is expressed primarily in placenta, bone marrow, and fetal liver/spleen and to a lesser extent in brain and CNS.
- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
- 10 not limited to, hematopoietic disorders; placental insufficiency; neurological disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and/or CNS, expression of this gene at significantly higher or lower
- 15 levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic cells and tissue, cells and tissue of the immune system, and neurological tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression
- 20 level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:113 as residues: Arg-53 to Gln-58.
- The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the proliferation, maintenance, and/or
- 25 differentiation of hematopoietic cells. In addition, it may be involved in the maintenance and establishment of the vasculature, and may play a role in the regulation of angiogenesis. Thus, it may play a role in the establishment and/or maintenance of tumors. Expression in the CNS indicates that this gene product may also be useful in the treatment of neurodegenerative disorders, such as Alzheimers Disease, Parkinsons
- 30 Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses , autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the
- 35 developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a

tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:41 and may have been publicly available prior to conception of the present invention.

- 5 Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1028 of SEQ ID NO:41, b is an integer of 15 to 1042, where
10 both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 32

The translation product of this gene was shown to have homology to the ras-related protein RABB from Dictyostelium discoideum (See Genebank Accession No.P34142). Members of the Ras family of proteins are known to be essential to normal cell cycle control and mutations of which have been shown to lead to the predisposition of cancer.

- This gene is expressed primarily in Jurkat T cells.
20 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, T cell lymphomas; defects in immune surveillance and/or T cell activation. Similarly, polypeptides and antibodies directed to these polypeptides are
25 useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken
30 from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- The tissue distribution combined with its homology to a Ras-related protein
35 indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of defects in immune surveillance and cancer. Expression of this gene

product in T cells indicates that it represents a secreted protein that may regulate T cells in an autocrine fashion, thereby impacting on their ability to recognize antigen and become activated, or may be involved in immune modulation. Likewise, this may represent a secreted protein made by T cells that affects other hematopoietic cells and

5 regulates their proliferation and/or differentiation. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:42 and may have been publicly available prior to

10 conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 688 of SEQ ID NO:42, b is

15 an integer of 15 to 702, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 33

The translation product of this gene shares sequence homology with a known

20 human spliceosome associated protein (See Genebank Accession No. AA523942) as well as a yeast protein (ORF YBR173c [Saccharomyces cerevisiae]). Preferred polypeptides comprise the following amino acid sequence:

MNARGLGSELKDSIPVTELSASGPFES
HDLLRKGFSCVKNELLPSHPLELSEKNFQLNQDKMNFSTLRNIQGLFAPLKLQ
25 MEFKAVQQVQRLPFLSSNLSLDVLRGNDETIGFEDILNDPSQSEVMGEPLMV
EYKLGLL (SEQ ID NO:166). Also preferred are the polynucleotides encoding these polypeptides.

This gene is expressed primarily in bone marrow and stromal cells, and to a lesser extent in T cells and peripheral blood cells.

30 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic disorders; leukemias; defects in immune surveillance; defects in T cell activation; inflammation; bacterial infections, and other disorders

35 characterized by immunodeficiency. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential

identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:115 as residues: Lys-16 to Thr-24.

5 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the proliferation, differentiation, and/or activation of hematopoietic cell lineages. Such treatments could involve chemoprotection or expansion of either progenitor cells or specific mature blood lineages. Likewise, this gene product could be involved in immune modulation, or in

10 15 affecting T cell activation and antigen recognition. Alternatively, the protein product of this gene is useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow

20 25 reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell

25 30 types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:43 and may have been publicly available prior to conception of the present invention. Preferably,

30 35 such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 628 of SEQ ID NO:43, b is an integer of 15 to 642, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 34

This gene maps to chromosome 4, and therefore, may be used as a marker in linkage analysis for chromosome 4.

- 5 This gene is expressed primarily in placenta and brain, and to a lesser extent in specific tumors and cancers (kidney, colorectal, colon, osteoclastoma).

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
10 not limited to, tumors of the kidney, colon, and bone; neurological disorders; defects of the vasculature. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vasculature and CNS, expression of this gene at significantly higher
15 or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, cells and tissue of the immune system, neural tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,
20 the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment of neurological disorders, such as Alzheimers or schizophrenia. Expression of this gene in the placenta may indicate a
25 role in fetal development, or may simply be a hallmark of expression in the vasculature. Expression of this gene product in endothelial cells may indicate secretion of the protein product into the circulation, where it may have effects on circulating blood cells, or on tissues at distant locations. At such sites, it may control cellular proliferation and/or differentiation. In addition, expression in a variety of tumors indicates that this gene
30 product may play a role in cellular proliferation. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:44 and may have been publicly available prior to
35 conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related

sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1205 of SEQ ID NO:44, b is an integer of 15 to 1219, where both a and b correspond to the positions of 5 nucleotide residues shown in SEQ ID NO:44, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 35

This gene is expressed primarily in macrophages, treated with GM-CSF. 10 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune deficiencies; susceptibility to bacterial infections; improper stimulation of lymphocyte pools. Similarly, polypeptides and antibodies directed to 15 these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded 20 tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:117 as residues: Arg-48 to Asn-56. 25 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the regulation and/or stimulation of hematopoietic cells, particularly the circulating lymphocytes. Macrophages are one of the front lines of immune defense, particularly against bacterial pathogens, and are able to secrete cytokines and proteins that affect other blood cells. Thus, this gene product 30 may be important in regulation of the immune system, in activation of hematopoietic cells, such as T cells; and may play a role in antigen recognition. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence 35 databases. Some of these sequences are related to SEQ ID NO:45 and may have been publicly available prior to conception of the present invention. Preferably, such related

- polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 423 of
- 5 SEQ ID NO:45, b is an integer of 15 to 437, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 36

- 10 This gene is expressed primarily in endothelial cells. Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation and circulatory system disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the circulatory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endothelial cells, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.
- 15 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of inflammatory disorders involving endothelial cells, such as sepsis, inflammatory bowel diseases, psoriasis, and rheumatoid arthritis as well as atherosclerosis, which can lead to strokes and heart attacks. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues
- 20
- 25
- 30
- 35

a-b, where a is any integer between 1 to 519 of SEQ ID NO:46, b is an integer of 15 to 533, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where the b is greater than or equal to a + 14.

5 FEATURES OF PROTEIN ENCODED BY GENE NO: 37

The translation product of this gene was shown to have homology to the human transducin(beta)-like 1 protein (See Genebank Accession No P38262).

This gene is expressed primarily in fetal lung and to a lesser extent in adult lung and breast.

10 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, respiratory system diseases, and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological
15 probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the respiratory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., pulmonary tissue, and cancerous and wounded tissues) or bodily fluids (e.g., pulmonary surfactant, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

20 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and disease affecting the lung such as lung cancer, emphysema, pulmonary edema, asthma, cystic fibrosis, and pulmonary emboli. Alternatively, the protein product of this gene may be useful in the detection, treatment, and/or prevention of various inflammatory conditions afflicting endothelial tissue such as the vasculature and cardiovascular systems. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or
25 immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:47 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To
30 list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence
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described by the general formula of a-b, where a is any integer between 1 to 1835 of SEQ ID NO:47, b is an integer of 15 to 1849, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where the b is greater than or equal to a + 14.

5

FEATURES OF PROTEIN ENCODED BY GENE NO: 38

This gene is expressed primarily in prostate cancer and to a lesser extent in osteoblasts.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, prostate cancer, osteoporosis. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal tissue, reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., seminal fluid, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in tumors of prostate origins indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of these tumors, in addition to other tissues where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:48 and may have been publicly available prior to conception of the present invention.

30 Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 912 of SEQ ID NO:48, b is an integer of 15 to 926, where 35 both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 39

The translation product of this gene was shown to have homology to the mdkk-1 protein from *Mus musculus* (See Genebank Accession No. gil2736292 (AF030433)) which has been shown to be important as a possible homeobox gene inducer specific to head development. One embodiment of this gene comprises polypeptides of the following amino acid sequence: GGNKYQTIDNYQPYP @ (SEQ ID NO:167), PLLGVSATLNSVLSNAIKN @ (SEQ ID NO:168), and/or GSAVSAAPGILYPG. An additional embodiment is the polynucleotides encoding these polypeptides (SEQ ID NO:169).

This gene is expressed primarily in placenta and to a lesser extent in smooth muscle.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental disorders of the fetus, and/or reproductive disorders, particularly of the female. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of developing tissues in the fetus, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution combined with the homology to a suspected homeobox domain inducer indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of developmental disorders, particularly those involving hematopoiesis and pattern formation in the embryo. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:49 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To

list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1579 of SEQ ID NO:49, b is an integer of 15 to 1593, where both a and b correspond to the 5 positions of nucleotide residues shown in SEQ ID NO:49, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 40

When tested against sensory neuron cell lines (PC12), supernatants removed 10 from cells containing this gene activated the early growth response gene 1 pathway (EGR1). Thus, it is likely that this gene activates neuronal cells through the Jak-STAT signal transduction pathway. EGR1 (early growth response gene 1) is a separate signal transduction pathway from Jak-STAT, genes containing the EGR1 promoter are induced in various tissues and cell types upon activation, leading the cells to undergo 15 differentiation and proliferation.

This gene is expressed primarily in neutrophils and to a lesser extent in pancreatic carcinoma.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a 20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation, gastrointestinal, and immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, 25 expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., 30 the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:122 as residues: Pro-8 to Ala-16.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of 35 immune system disorders. Expression of this gene product in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of

potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin,

5 the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, and leukemia. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have

10 commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through

15 sequence databases. Some of these sequences are related to SEQ ID NO:50 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a

20 nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 964 of SEQ ID NO:50, b is an integer of 15 to 978, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where the b is greater than or equal to a + 14.

25 **FEATURES OF PROTEIN ENCODED BY GENE NO: 41**

This gene is expressed primarily in breast lymph node and to a lesser extent in anergic T-cell.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

30 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation, and immunodeficiency disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of

35 this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and

wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

- 5 The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product
10 may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune
15 deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in
20 the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:51 and may have been
25 publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 419 of
30 SEQ ID NO:51, b is an integer of 15 to 433, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 42

- 35 This gene is expressed primarily in synovium.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation and diseases of the joints. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and connective tissue, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of inflammatory disorders, particularly those involving the joints and skeletal system, such as rheumatoid arthritis and in particular the connective tissues (e.g. trauma, tendonitis, chondromalacia). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. .

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:52 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 847 of SEQ ID NO:52, b is an integer of 15 to 861, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where the b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 43

This gene maps to chromosome 5, and therefore, may be used as a marker in linkage analysis for chromosome 5.

35

This gene is expressed primarily in synovium.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

- biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the joints and connective tissues. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders
- 5 of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal tissue, and cancerous and wounded tissues) or bodily fluids (e.g. serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene
- 10 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of inflammatory joint disorders as well as suggest a role in the detection and treatment of disorders and

15 conditions affecting the skeletal system, in particular the connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation). Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:53 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence

20 described by the general formula of a-b, where a is any integer between 1 to 496 of SEQ ID NO:53, b is an integer of 15 to 510, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where the b is greater than or equal to a + 14.

30 **FEATURES OF PROTEIN ENCODED BY GENE NO: 44**

This gene is expressed primarily in activated T cells. Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation and other immune system disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing

- immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and
- 5 cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID
- 10 NO:126 as residues: Met-1 to Lys-7.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of

15 potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also

20 used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in

25 the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence

30 databases. Some of these sequences are related to SEQ ID NO:54 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence

35 described by the general formula of a-b, where a is any integer between 1 to 295 of SEQ ID NO:54, b is an integer of 15 to 309, where both a and b correspond to the

positions of nucleotide residues shown in SEQ ID NO:54, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 45

- 5 This gene is expressed primarily in placenta, liver, lung, endometrial stromal cell and embryo.
- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions such as cancers, 10 immunodeficiency and autoimmune diseases, as well as reproductive and hepatic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may 15 be routinely detected in certain tissues or cell types (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not 20 having the disorder.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In 25 addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly 30 available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:55 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more 35 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1571 of SEQ ID NO:55, b is an integer of 15

to 1585, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 46

- 5 This gene is expressed primarily in placenta, amniotic cells and adrenal gland tumor.
- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions such as cancers, as well
- 10 10 as various reproductive and endocrine disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell
- 15 15 types (e.g., endocrine tissue, reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include
- 20 20 those comprising a sequence shown in SEQ ID NO:128 as residues: Cys-52 to Val-61.

The tissue distribution within placenta and amniotic tissues indicates that polynucleotides and polypeptides corresponding to this gene useful for the treatment and diagnosis of reproductive disorders, particularly those of the female reproductive system, including cancer and tissues characteristic of the developing embryo. In

25 25 addition, the tissue distribution within the adrenal gland indicates that the protein product of this gene is useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:56 and

30 30 35 may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the

present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 860 of SEQ ID NO:56, b is an integer of 15 to 874, where 5 both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 47

This gene is expressed primarily in melanocyte, melanoma, dendritic cells and 10 fetal brain.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, skin disorders, particularly melanoma, as well as neurodegenerative 15 disorders and cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell 20 types (e.g., neural tissue, integumentary tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those 25 comprising a sequence shown in SEQ ID NO:129 as residues: Lys-76 to Gly-81.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e. 30 keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e., wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, uticaria, eczema, photosensitivity, autoimmune disorders (i.e. lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, 35 pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. Moreover, such disorders may predispose increased susceptibility to viral

and bacterial infections of the skin (i.e. cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athletes foot, and ringworm). Alternatively, the tissue distribution within dendritic cells and fetal brain indicates that the protein product of this gene is useful for the detection/treatment
5 of neurodegenerative disease states and behavioral disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses , autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product
10 may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available
15 and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:57 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
Accordingly, preferably excluded from the present invention are one or more
20 polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1155 of SEQ ID NO:57, b is an integer of 15 to 1169, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where the b is greater than or equal to a + 14.

25 FEATURES OF PROTEIN ENCODED BY GENE NO: 48

This gene maps to chromosome 1, and therefore, may be used as a marker in linkage analysis for chromosome 1.

This gene is expressed primarily in ovary tumors and to a lesser extent in breast, placenta, pineal gland, infant brain, T cell and B cell lymphoma.

30 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, ovary cancer, reproductive disorders, particularly of the female reproductive system, as well as disorders of the immune system, including lymphoma
35 and immunodeficiencies. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential

identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and female reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, endocrine tissue, cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, lymph, breast milk, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:130 as residues: Asn-33 to Lys-38.

The tissue distribution in tumors of the ovary and lymph nodes, as well as, in breast and placental tissues indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of such tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues. Alternatively, The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:58 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present

invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1052 of SEQ ID NO:58, b is an integer of 15 to 1066, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 49

This gene is expressed primarily in breast tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., breast tissue and cancerous and wounded tissues) or bodily fluids (e.g., breast milk, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:131 as residues: Ala-40 to Trp-45.

The tissue distribution in breast tissue indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of tumors within this tissue. Alternatively, the expression in breast may suggest that the protein product of this gene is useful for the diagnosis, treatment, and/or prevention of various reproductive system disorders, particularly of the female reproductive system. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:59 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides

comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 758 of SEQ ID NO:59, b is an integer of 15 to 772, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where the b is greater than or equal to a + 14.

5

FEATURES OF PROTEIN ENCODED BY GENE NO: 50

This gene is expressed primarily in fetal liver, retina and to a lesser extent in thyroid and pineal gland.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hepatic and endocrine disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoiesis and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., liver, endocrine tissue, and cancerous and wounded tissues) or bodily fluids (e.g., bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:132 as residues: Lys-9 to Trp-14.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Alternatively, expression in pineal and thyroid glands indicates that the protein product of this gene is useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g. diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g. hyper-, hypothyroidism), parathyroid (e.g. hyper-, hypoparathyroidism), hypothalamus, and testes. Protein, as well as, antibodies

directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:60 and may have been publicly available
5 prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1184 of SEQ ID NO:60, b
10 is an integer of 15 to 1198, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 51

15 The translation product of this gene shares sequence homology with seizure-related gene product 6 type 2 precursor which is a novel, brain-specific, gene thought to be important in the predisposition of seizures (See Genebank Accession No.gnl|PID|d1006729). One embodiment of this gene comprises polypeptides of the following amino acid sequence: AGIQHELACDNPGLPENGYQILYKRLYLPGESLT
20 FMCYEGFELMGEVTIRCILGQPSHWNGPLPVCKVAE AAAETSLEGGN @ (SEQ ID NO:170) QPSHWNGPLPVCKVAEAAAETSLEGGN @ (SEQ ID NO:171), and/or YETGETREYEVSI (SEQ ID NO:172). An additional embodiment is the polynucleotides encoding these polypeptides.

This gene is expressed primarily in brain.

25 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, seizures and other neural and CNS disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample
30 taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an
35

individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:133 as residues: Cys-26 to Leu-32, Thr-49 to Ile-55, Glu-57 to Glu-63.

The tissue distribution in brain combined with its homology to a putative seizure gene indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of seizures and epilepsy, including neurodegenerative disease states and behavioral disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses , autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:61 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 544 of SEQ ID NO:61, b is an integer of 15 to 558, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 52

When tested against PC12 cell lines, supernatants removed from cells containing this gene activated the EGR1 (early growth response 1) pathway. Thus, it is likely that this gene activates sensory neuron cells through the EGR1 signal transduction pathway. EGR1 is a separate signal transduction pathway from Jak-STAT, genes containing the EGR1 promoter are induced in various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation.

This gene is expressed primarily in fetal brain.
Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological disorders, particularly of the developing embryo. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For 5 a number of disorders of the above tissues or cells, particularly of the fetal brain and CNS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues (serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or 10 bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:134 as residues: Arg-16 to Thr-35.

The tissue distribution in fetal brain combined with the detected biological activity within sensory neurons indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative 15 disease states and behavioral disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a 20 role in the treatment and/or detection of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many 25 polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:62 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, 30 preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 602 of SEQ ID NO:62, b is an integer of 15 to 616, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where the b is greater than or equal to a + 14.

35 **FEATURES OF PROTEIN ENCODED BY GENE NO: 53**

This gene is expressed primarily in frontal cortex, and schizophrenoid brain tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a

- 5 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, Schizophrenia, and other neurodegenerative disorders, including cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the
10 brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or
15 bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:135 as residues: Asp-65 to Asn-72.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimers Disease, Parkinsons

- 20 Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses , autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the
25 developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:63 and
30 may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is
35 any integer between 1 to 797 of SEQ ID NO:63, b is an integer of 15 to 811, where

both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 54

- 5 This gene is expressed primarily in osteoclastoma, gall bladder, and infant brain.
- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, Osteoclastoma, and gastrointestinal, skeletal, and neural disorders, particularly cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the bone, expression of this gene at significantly higher 10 or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal tissue, neural tissue, and cancerous and wounded tissues) or bodily fluids (e.g., bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an 15 individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:136 as residues: Gly-23 to His-30.

The tissue distribution in osteoclastoma cells indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection, treatment, and/or prevention of various skeletal system disorders, particularly bone cancer. Moreover, the 20 tissue distribution within the gall bladder indicates that the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental 25 abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Osteoclastoma, Gall Bladder tumor. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:64 and may have been publicly available prior to conception of the present invention. Preferably, 30 such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably 35

excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 979 of SEQ ID NO:64, b is an integer of 15 to 993, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where
5 the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 55

The translation product of this gene shares sequence homology with b cell growth factor which is thought to be important in B cell development.

10 This gene is expressed primarily in breast lymph node and primary dendritic cells

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are
15 not limited to, immune disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell
20 types (e.g., cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include
25 those comprising a sequence shown in SEQ ID NO:137 as residues: Ser-39 to Tyr-46.

The tissue distribution combined with its homology to a B-cell growth factor indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in lymph nodes indicates a role in the regulation of the proliferation;
30 survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved
35 in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS,

leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem

5 cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences

10 are related to SEQ ID NO:65 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general

15 formula of a-b, where a is any integer between 1 to 675 of SEQ ID NO:65, b is an integer of 15 to 689, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 56

20 The translation product of this gene shares sequence homology with small hepatocellular oncoprotein which is thought to be important in liver development (See Genebank Accession No. R07057). This gene maps to chromosome 20, and therefore, may be used as a marker in linkage analysis for chromosome 20.

This gene is expressed primarily in monocytes.

25 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, liver disorders, particularly hepatoma. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes

30 for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and digestive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., haematopoetic cells and tissue, liver, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial

35 fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level

in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:138 as residues: Met-17 to Lys-32.

The homology to a hepatocellular oncogene indicates that polynucleotides and polypeptides corresponding to this gene are useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). The expression also indicates a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various would-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Alternatively, The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are . useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:66 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 928 of SEQ ID NO:66, b is an integer of 15 to 942, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 57

The translation product of this gene was shown to have homology to the human proteins myotubularin related protein 3 and NTII-1 nerve protein (See Genebank

Accession Nos. gil1378120 and R99800, respectively) which are both thought to play important roles as growth factors in muscle and nerve tissue, respectively. Preferred polypeptides comprise the following amino acid sequence:

DDDGLPFPTDVIQHRLRQIEAGYKQEVEQLRR

- 5 QVRDSDEXGHPSLLCPSSRAPMDYEDDFTCLKESDGSDTEFGSDHSEDCLSEA
SWEPVDKKETEVTRWVPDHMASHCYNCDCEFWLAKRRHCRNCGNVFCAG
CCHLKLPIPDLQQLYDPVLVCNSCYXTHSSLSCQGTHEPTAEETHCYSFQLNAGE
KPVQF (SEQ ID NO:173), SEASWEPVDKKETEVTRWVPDHMASHCY (SEQ ID
NO:174), HHCRNCGNVF (SEQ ID NO:175, and/or RLRQIEAGYKQEVE (SEQ ID
10 NO:176). Also preferred are the polynucleotides encoding these polypeptides.

This gene is expressed primarily in bone, spleen, brain, apoptotic T cells, hypothalamus, and other immune cells.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune system, musculoskeletal, and neural disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous 20 and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an 25 individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:139 as residues: Glu-63 to Asp-68.

- The tissue distribution in neural tissue combined with the homology to a nerve growth factor indicates that polynucleotides and polypeptides corresponding to this 30 gene are useful for the detection/treatment of neurodegenerative disease states and behavioral disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses , autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and 35 perception, as well as neuromuscular disorders such as MS and muscular dystrophy. In addition, the gene or gene product may also play a role in the treatment and/or detection

of developmental disorders associated with the developing embryo, sexually-linked disorders, or disorders of the cardiovascular system. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST 5 sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:67 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention 10 are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2295 of SEQ ID NO:67, b is an integer of 15 to 2309, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where the b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 58

This gene is expressed primarily in ovary.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a 20 biological sample and for diagnosis of diseases and conditions which include, but are not limited to, ovarian cancer, and other disorders that afflict the female reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the 25 female reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene 30 expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:140 as residues: Pro-23 to Gly-54.

The tissue distribution in tumors the ovary indicates that polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and intervention of 35 these tumors, in addition to other tumors where expression has been indicated. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific

marker and/or immunotherapy target for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:68 and may have been publicly available prior to conception of the present invention. Preferably,

5 such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 800 of SEQ ID NO:68, b is an integer of 15 to 814, where both a and b

10 correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 59

This gene is expressed primarily in ovary.

15 Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, ovarian cancer, and other disorders afflicting the female reproductive system. Similarly, polypeptides and antibodies directed to these polypeptides are useful

20 in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive tissue, and cancerous and wounded tissues) or bodily fluids (e.g., amniotic fluid, serum, plasma,

25 urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

The tissue distribution in ovarian tissue indicates that polynucleotides and

30 polypeptides corresponding to this gene are useful for diagnosis and intervention of ovarian tumors, in addition to other tumors of the female reproductive system. Protein, as well as, antibodies directed against the protein may show utility as a tissue-specific marker and/or immunotherapy target for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through

35 sequence databases. Some of these sequences are related to SEQ ID NO:69 and may have been publicly available prior to conception of the present invention. Preferably,

such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer 5 between 1 to 774 of SEQ ID NO:69, b is an integer of 15 to 788, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where the b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 60

When tested against PC12 cell lines, supernatants removed from cells containing this gene activated the EGR1 (early growth response 1) pathway. Thus, it is likely that this gene activates sensory neuronal cells through the EGR1 signal transduction pathway. EGR1 is a separate signal transduction pathway from Jak-STAT, genes containing the EGR1 promoter are induced in various tissues and cell 10 types upon activation, leading the cells to undergo differentiation and proliferation.

This gene is expressed primarily in osteoblast.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are 20 not limited to, skeletal disorders, particular bone cancer. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the Bone, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell 25 types (e.g., skeletal tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a 30 sequence shown in SEQ ID NO:142 as residues: Tyr-20 to Lys-31.

In addition the expression of this gene product in synovium would suggest a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation) as well as in the 35 diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation,

- andspecific joint abnormalities as well as chondrodysplasias i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above
- 5 listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:70 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
- 10 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 777 of SEQ ID NO:70, b is an integer of 15 to 791, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where the b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 61

- This gene is expressed primarily in adipocyte. Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, obesity. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., adipose tissue, and cancerous and wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:143 as residues: His-2 to Leu-8.

The tissue distribution would suggest that polynucleotides and polypeptides corresponding to this gene are useful in the diagnosis, treatment, and/or prevention of obesity and lipid metabolism disorders. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are

publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:71 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is 5 cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 790 of SEQ ID NO:71, b is an integer of 15 to 804, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where the b is greater than or equal to a + 14.

10

FEATURES OF PROTEIN ENCODED BY GENE NO: 62

When tested against Jurkat T-cell lines, supernatants removed from cells containing this gene activated the GAS (gamma activation site) pathway. Thus, it is likely that this gene activates T-cells through the Jak-STAT signal transduction 15 pathway. GAS is a promoter element found upstream in many genes which are involved in the Jaks-STAT pathway. The Jaks-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells.

This gene is expressed primarily in synovial tissue.

Therefore, polynucleotides and polypeptides of the invention are useful as 20 reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, chronic synovitis, immune. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of 25 the above tissues or cells, particularly of the immune system expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and skeletal tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having 30 such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:144 as residues: Pro-74 to Lys-82.

The biological assay results indicating activity in Jurkat T-cells for the protein 35 product of this gene indicates that polynucleotides and polypeptides corresponding to this gene useful for the diagnosis and treatment of a variety of immune system

disorders. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene has been shown to activate genes in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues.

5 In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. In addition the expression of this gene product in synovial tissues indicates a role for this protein in the detection and treatment of disorders and conditions affecting the skeletal system, in particular the connective

10 tissues (e.g. arthritis, trauma, tendonitis, chondromalacia and inflammation) as well as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias i.e. spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type

15 II, metaphyseal chondrodysplasia type Schmid. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. . Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:72 and may have been publicly available prior to

20 conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 769 of SEQ ID NO:72, b is

25 an integer of 15 to 783, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where the b is greater than or equal to a + 14.

30

FEATURES OF PROTEIN ENCODED BY GENE NO: 63

The translation product of this gene shares sequence homology with fetal troponin which is known to be essential for normal muscular function in all skeletal and cardiovascular muscles.

This gene is expressed primarily in melanocytes, fetal liver, brain, testes, spleen, and placenta.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, melanoma, neuromuscular disorders, such as multiple sclerosis, and endothelial-related diseases. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., muscle, endothelial cells and tissue, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:145 as residues: Ala-27 to Leu-36, Phe-40 to Leu-50.

The tissue distribution and homology to troponin indicates that polynucleotides and polypeptides corresponding to this gene are useful for treatment, diagnosis, and/or prevention of various neuromuscular disorders such as MS, muscular dystrophy, cardiomyopathy, myositis, myomas, leiomyomas, rhabdomyosarcomas, and coronary heart disease. Alternatively, the expression in a variety of fetal immune tissues indicates that the protein product of this gene is useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in spleen and fetal liver indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this

gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

- 5 Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:73 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.
- 10 Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1509 of SEQ ID NO:73, b is an integer of 15 to 1523, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where the b is greater than or equal to a + 14.

15

FEATURES OF PROTEIN ENCODED BY GENE NO: 64

- The translation product of this gene shares sequence homology with small hepatocellular oncoprotein gene which is thought to be important in liver disorders (See Genebank Accession No. R07057). One embodiment of this gene comprises polypeptides of the following amino acid sequence:
- MSHCARPLFFETFFILLSPRLKCSGTNTVHYSLLGSSNSASVPQVGGLTNAQ
HDTWLIFVFCVCVCEPLRRPWAALISVTSSIK (SEQ ID NO:177), and/or
VPQVGGLTNAQHDTWLIFVFCVCVCEPLRR (SEQ ID NO:178). An additional embodiment is the polynucleotides encoding these polypeptides.
- 25 This gene is expressed primarily in neutrophils, hemangiopericytoma, activated T cells.

- Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hepatic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatoma and immune system disorder, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cells and tissue of the immune system, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine,

synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred epitopes include those comprising a sequence shown in SEQ ID NO:146 as residues: Arg-20 to Gly-25.

The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis and treatment of a variety of immune system disorders. Expression of this gene product in neutrophils and T-cells indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions.

Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tumors and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the homology to a hepatic oncogene indicates that the protein product of this gene is useful for the detection and treatment of liver disorders and cancers (e.g. hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition, the expression would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various wound-healing models and/or tissue trauma. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:74 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of

a-b, where a is any integer between 1 to 744 of SEQ ID NO:74, b is an integer of 15 to 758, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where the b is greater than or equal to a + 14.

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	NT SEQ ID NO: X	NT Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	NT SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of Secreted Portion
1	HSXBV35	209138 07/03/97	Uni-ZAP XR	11 558	1	558	106	106	83	1	19	20
2	HTEDF42	209138 07/03/97	Uni-ZAP XR	12 715	82	715	115	115	84	1	29	30
3	HTGAW51	209138 07/03/97	Uni-ZAP XR	13 838	1	838	41	41	85	1	44	45
4	HTLBG08	209138 07/03/97	Uni-ZAP XR	14 513	1	513	117	117	86	1	25	26
5	HTLFE42	209138 07/03/97	Uni-ZAP XR	15 712	1	712	116	116	87	1	22	23
6	HTSEW17	209138 07/03/97	pBluescript	16 652	1	652	170	170	88	1	35	36
7	HTWFK09	209138 07/03/97	pSport1	17 742	1	742	378	378	89	1	18	19
8	HTXDJ88	209138 07/03/97	Uni-ZAP XR	18 1219	111	913	162	162	90	1	28	29
9	HUSGC54	209138 07/03/97	pSport1	19 874	1	874	148	148	91	1	42	43
10	HWTAD49	209138 07/03/97	Uni-ZAP XR	20 464	110	464	149	149	92	1	48	49
11	HWTBK81	209138 07/03/97	Uni-ZAP XR	21 637	78	635	139	139	93	1	23	24
12	HACBHI6	209138 07/03/97	Uni-ZAP XR	22 752	1	752	27	27	94	1	37	38
13	HCUDE16	209138 07/03/97	ZAP Express	23 492	1	454	104	104	95	1	24	25

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	NT SEQ ID NO: X	NT Total Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT First AA of Signal Pep.	NT First AA of ID NO: Y	AA SEQ	First AA Sig Pep.	Last AA Sig Pep.	First AA Secreted Portion	Last AA of ORF
14	HHEPT60	209138 07/03/97	pCMV Sport 3.0	24	532	21	532	245	245	96	1	18	19
15	HLWBZ73	209138 07/03/97	pCMV Sport 3.0	25	920	352	905	434	434	97	1	28	29
16	HNGFR75	209138 07/03/97	Uni-ZAP XR	26	917	1	917	54	54	98	1	23	24
17	HNHEO73	209138 07/03/97	Uni-ZAP XR	27	662	1	662	84	84	99	1	28	29
18	HNHFO29	209138 07/03/97	Uni-ZAP XR	28	699	1	699	160	160	100	1	21	22
19	HONAH29	209138 07/03/97	pBluescript SK-pSport	29	1637	17	1632	144	144	101	1	25	26
20	HGCAB62	209138 07/03/97	pSport	30	2142	1223	2109	110	110	102	1	47	48
20	HGCAB62	209138 07/03/97	pSport	75	1096	209	1096	406	406	147	1	41	42
21	HAQBI01	209138 07/03/97	Uni-ZAP XR	31	1564	1084	1564	231	231	103	1	19	20
21	HAQBI01	209138 07/03/97	Uni-ZAP XR	76	1230	406	1171	637	637	148	1	20	21
22	HCMSW93	209139 07/03/97	Uni-ZAP XR	32	1631	254	855	362	362	104	1	25	26
23	HDPBA48	209139 07/03/97	pCMV Sport 3.0	33	978	1	978	478	478	105	1	48	49
23	HDPBA48	209139 07/03/97	pCMV Sport 3.0	77	911	1	911	309	309	149	1	12	13
												17	

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	NT SEQ ID NO: X	5' NT of Total Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	AA SEQ ID NO: Y	First AA Sig Pep	Last AA Sig Pep	First AA Sig Pep	Last AA Sig Pep	First AA Secreted Portion	Last AA Secreted Portion
37	HPEBT96	209139 07/03/97	Uni-ZAP XR	47	1849	812	1517	968	968	119	1	37	38
38	HPFCE63	209139 07/03/97	Uni-ZAP XR	48	926	203	926	414	414	120	1	17	18
39	HPMBZ15	209139 07/03/97	Uni-ZAP XR	49	1593	182	1593	1124	1124	121	1	49	50
39	HPMBZ15	209139 07/03/97	Uni-ZAP XR	78	488	20	488	121	121	150	1		15
40	HROAE16	209139 07/03/97	Uni-ZAP XR	50	978	1	978	209	209	122	1	32	33
41	HSAYM40	209139 07/03/97	Uni-ZAP XR	51	433	1	433	190	190	123	1	19	20
42	HSNAD72	209139 07/03/97	Uni-ZAP XR	52	861	1	861	220	220	124	1	22	23
43	HSNAU78	209139 07/03/97	Uni-ZAP XR	53	510	1	510	89	89	125	1	17	18
44	HTBAB28	209139 07/03/97	Uni-ZAP XR	54	309	1	309	43	43	126	1	35	36
45	HALSQ38	209141 07/09/97	Uni-ZAP XR	55	1585	741	1585	776	776	127	1	17	18
46	HAQBT52	209141 07/09/97	Uni-ZAP XR	56	874	20	874	136	136	128	1	47	48
47	HBIBL04	209141 07/09/97	Uni-ZAP XR	57	1169	5	753	726	726	129	1	40	41
47	HBIBL04	209141 07/09/97	Uni-ZAP XR	79	753	1	749	228	228	151	1	21	22
													21

	Gene No.	ATCC Deposit Nr and Date	cDNA Clone ID	NT SEQ ID NO: X	NT Total NT Seq. No:	5' NT of Clone Seq.	3' NT of Seq.	5' NT of First AA of Signal Pep.	NT SEQ ID NO: Y	AA SEQ ID NO: Y	First AA Sig Pep.	Last AA Sig Pep.	First AA Secreted Portion	Last AA Secreted Portion
48	HBJCI95	209141 07/09/97	Uni-ZAP XR	58	1066	1	1066	188	188	130	1	12	13	63
49	HBNBQ61	209141 07/09/97	Uni-ZAP XR	59	772	1	772	88	88	131	1			36
50	HE2ID06	209141 07/09/97	Uni-ZAP XR	60	1198	534	1198	715	715	132	1	28	29	40
51	HEBCM63	209141 07/09/97	Uni-ZAP XR	61	558	1	558	246	246	133	1	26	27	68
52	HFFAK76	209141 07/09/97	Lambda ZAP II	62	616	1	616	150	150	134	1	17	18	47
53	HFRBF28	209141 07/09/97	Uni-ZAP XR	63	811	1	811	57	57	135	1	16	17	16
54	HGBHM89	209141 07/09/97	Uni-ZAP XR	64	993	1	970	49	49	136	1	28	29	54
55	HLMBP18	209141 07/09/97	Lambda ZAP II	65	689	1	689	398	398	137	1			14
56	HMSSEL55	209141 07/09/97	Uni-ZAP XR	66	942	1	942	437	437	138	1	18	19	35
57	HMWCF89	209141 07/09/97	Uni-Zap XR	67	2309	1609	2308	1216	1216	139	1	23	24	80
57	HMWCF89	209141 07/09/97	Uni-Zap XR	80	2138	1435	2138	1467	1467	152	1	22	23	24
58	HODAZ55	209141 07/09/97	Uni-ZAP XR	68	814	1	814	37	37	140	1	16	17	24
59	HODDF08	209141 07/09/97	Uni-ZAP XR	69	788	1	788	141	141	141	1	32	33	50

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	NT SEQ ID NO: X	5' NT of Total NT Seq.	3' NT of Clone Seq.	5' NT of Clone Seq.	Start Codon	5' NT of First AA of Signal Pep.	AA SEQ ID NO: Y	First AA of Sig Pep.	Last AA of Sig Pep.	First AA of Secreted Portion	Last AA of Secreted Portion	First AA of ORF
60	HOSDK95	209141 07/09/97	Uni-ZAP XR	70	791	1	791	121	121	142	1	28	29	29
61	HOUAR65	209141 07/09/97	Uni-ZAP XR	71	804	1	804		53	143	1	28	29	49
62	HSVACT7	209141 07/09/97	Uni-ZAP XR	72	783	1	783	27	27	144	1	28	29	86
63	HJAAT30	209141 07/09/97	pBluescript SK-	73	1523	767	1448	855	855	145	1	23	24	57
63	HJAAT30	209141 07/09/97	pBluescript SK-	81	1327	71	750	386	386	153	1	39	40	40
64	HNECF34	209141 07/09/97	Uni-ZAP XR	74	758	1	758	106	106	146	1	23	24	87
64	HNECF34	209141 07/09/97	Uni-ZAP XR	82	758	1	758	269	269	154	1	17	18	24

Table 1 summarizes the information corresponding to each "Gene No." described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA clone ID" identified in Table 1 and, in some cases, from additional related DNA clones. The 5 overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain 10 multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in the cDNA Clone ID.

"Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No." The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT 15 of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as "5' NT of Start Codon." Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as "5' NT of First AA of Signal Pep."

The translated amino acid sequence, beginning with the methionine, is identified 20 as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as "First AA of Sig Pep" and "Last AA of Sig Pep." The predicted 25 first amino acid position of SEQ ID NO:Y of the secreted portion is identified as "Predicted First AA of Secreted Portion." Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as "Last AA of ORF."

SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and 30 otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic 35 methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to the secreted proteins encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are species homologs. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for the desired homologue.

The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below).

It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

- 5 The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988).
Polypeptides of the invention also can be purified from natural or recombinant sources
10 using antibodies of the invention raised against the secreted protein in methods which are well known in the art.

Signal Sequences

- Methods for predicting whether a protein has a signal sequence, as well as the
15 cleavage point for that sequence, are available. For instance, the method of McGeoch, Virus Res. 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, Nucleic Acids Res. 14:4683-4690 (1986) uses the information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1
20 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, *supra*.) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

- In the present case, the deduced amino acid sequence of the secreted polypeptide
25 was analyzed by a computer program called SignalP (Henrik Nielsen et al., Protein Engineering 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results
30 shown in Table 1.

- As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty. Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., +
35 or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely

uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

10 Polynucleotide and Polypeptide Variants

"Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

15 By a polynucleotide having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the polynucleotide is identical to the reference sequence except that the polynucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a polynucleotide having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence shown in Table 1, the ORF 20 (open reading frame), or any fragment specified as described herein.

25 As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between 30 a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result 35 of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization

Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query

amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions,
5 interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequences shown in Table 1 or to the amino acid sequence encoded by deposited DNA clone can be
10 determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. (1990) 6:237-245). In a sequence alignment the query and
15 subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window
20 Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity.
25 For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of
30 the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are
35 considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

- For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired
- 5 residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence.
- 10 This time the deletions are internal deletions so there are no residues at the N- or C- termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query
- 15 sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or

20 activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in

25 the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level.

30 Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be

35 deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., J. Biol. Chem. 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after

deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1 α . They used random mutagenesis to generate over 3,500 individual IL-1 α mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham 5 and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the 10 protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues 15 Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, 20 where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino 25 acids, such as an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins 30 with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence contained in the deposited clone or shown in SEQ ID NO:X. The short nucleotide fragments are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, 5 and even more preferably, at least about 40 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in the deposited clone or the nucleotide sequence shown in SEQ ID NO:X. These nucleotide fragments are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 10 nucleotides) are preferred.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments having a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 15 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:X or the cDNA contained in the deposited clone. In this context "about" includes the particularly recited ranges, larger 20 or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed herein.

In the present invention, a "polypeptide fragment" refers to a short amino acid sequence contained in SEQ ID NO:Y or encoded by the cDNA contained in the 25 deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding 30 region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

Preferred polypeptide fragments include the secreted protein as well as the 35 mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-

60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred.

- 5 Similarly, polynucleotide fragments encoding these polypeptide fragments are also preferred.

Particularly, N-terminal deletions of the polypeptide of the present invention can be described by the general formula m-p, where p is the total number of amino acids in the polypeptide and m is an integer from 2 to (p-1), and where both of these integers (m

- 10 & p) correspond to the position of the amino acid residue identified in SEQ ID NO:Y.

Moreover, C-terminal deletions of the polypeptide of the present invention can also be described by the general formula 1-n, where n is an integer from 2 to (p-1), and again where these integers (n & p) correspond to the position of the amino acid residue identified in SEQ ID NO:Y.

- 15 The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO:Y, where m and n are integers as described above.

- Also preferred are polypeptide and polynucleotide fragments characterized by
20 structural or functional domains, such as fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions.
25 Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotide fragments encoding these domains are also contemplated.

- Other preferred fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an
30 activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Epitopes & Antibodies

- In the present invention, "epitopes" refer to polypeptide fragments having
35 antigenic or immunogenic activity in an animal, especially in a human. A preferred embodiment of the present invention relates to a polypeptide fragment comprising an epitope, as well as the polynucleotide encoding this fragment. A region of a protein

molecule to which an antibody can bind is defined as an "antigenic epitope." In contrast, an "immunogenic epitope" is defined as a part of a protein that elicits an antibody response. (See, for instance, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983).)

5 Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

10 In the present invention, antigenic epitopes preferably contain a sequence of at least seven, more preferably at least nine, and most preferably between about 15 to about 30 amino acids. Antigenic epitopes are useful to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe, J. G. et al., Science 219:660-666 (1983).)

15 Similarly, immunogenic epitopes can be used to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow, M. et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle, F. J. et al., J. Gen. Virol. 66:2347-2354 (1985).) A preferred immunogenic epitope includes the secreted protein. The immunogenic epitopes may be presented together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse) or, if it is long enough (at least about 25 amino acids), without a carrier. However, 20 immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting.)

25 As used herein, the term "antibody" (Ab) or "monoclonal antibody" (Mab) is meant to include intact molecules as well as antibody fragments (such as, for example, Fab and F(ab')2 fragments) which are capable of specifically binding to protein. Fab and F(ab')2 fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody. (Wahl et al., J. Nucl. Med. 24:316-325 (1983).) Thus, these fragments are preferred, as well as the products of a FAB or other immunoglobulin expression library. 30 Moreover, antibodies of the present invention include chimeric, single chain, and humanized antibodies.

Fusion Proteins

35 Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein

by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention 5 include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

Moreover, fusion proteins may also be engineered to improve characteristics of 10 the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the 15 polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

Moreover, polypeptides of the present invention, including fragments, and 20 specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life *in vivo*. One reported example 25 describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., *Nature* 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., *J. Biochem.* 270:3958-3964 (1995).)

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion 30 proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for 35 example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D.

Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In 5 preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. 10 Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

15 Vectors, Host Cells, and Protein Production

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the 20 latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then 25 transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The 30 expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one 35 selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance

genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells; insect cells such as *Drosophila S2* and *Spodoptera Sf9* cells; animal cells such as CHO, COS, 5 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and 10 ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium 15 phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., *Basic Methods In Molecular Biology* (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

20 A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most 25 preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention, and preferably the secreted form, can also 30 be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial 35 modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein

after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

5

Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

10

The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

15

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

20

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include *in situ* hybridization, prescreening with labeled flow-sorted chromosomes, and preselection by hybridization to construct chromosome specific-cDNA libraries.

25

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence *in situ* hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

30

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes). Preferred polynucleotides correspond to the noncoding regions of the cDNAs because the coding sequences are

more likely conserved within gene families, thus increasing the chance of cross hybridization during chromosomal mapping.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage 5 analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library).) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease 10 could be one of 50-500 potential causative genes.

Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural 15 alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic 20 polypeptide can be used for further linkage analysis.

Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using 25 polynucleotides of the present invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Both methods rely on binding of the polynucleotide to DNA or RNA. For these techniques, preferred 30 polynucleotides are usually 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off 35 of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model

systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of

unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for 5 contamination.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers 10 for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

Each of the polypeptides identified herein can be used in numerous ways. The 15 following description should be considered exemplary and utilizes known techniques.

A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. (Jalkanen, M., et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell. Biol. 105:3087-20 3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and 25 technetium (99mTc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying secreted protein levels in a biological sample, proteins can also be detected *in vivo* by imaging. Antibody labels or markers for *in vivo* imaging of protein include those detectable by X-radiography, NMR or ESR. For X-30 radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

35 A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, 131I, 112In, 99mTc), a radio-opaque substance, or a material detectable by nuclear magnetic

resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human 5 subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc . The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The 10 Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene 15 expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder.

Moreover, polypeptides of the present invention can be used to treat disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to 20 supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B), to inhibit the activity of a polypeptide (e.g., an oncogene), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired 25 response (e.g., blood vessel growth).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such 30 as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a 35 recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

Biological Activities

The polynucleotides and polypeptides of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides could be used to treat the associated disease.

Immune Activity

A polypeptide or polynucleotide of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells

from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, a polynucleotide or polypeptide of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

A polynucleotide or polypeptide of the present invention may be useful in treating or detecting deficiencies or disorders of hematopoietic cells. A polypeptide or polynucleotide of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

Moreover, a polypeptide or polynucleotide of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotide or polypeptide of the present invention could be used to treat blood coagulation disorders (e.g., afibrinogenemia, factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, a polynucleotide or polypeptide of the present invention that can

decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

- A polynucleotide or polypeptide of the present invention may also be useful in
- 5 treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation,
- 10 differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Examples of autoimmune disorders that can be treated or detected by the present invention include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuropathy, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by a polypeptide or polynucleotide of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

25 A polynucleotide or polypeptide of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The

30 administration of a polypeptide or polynucleotide of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

35 Similarly, a polypeptide or polynucleotide of the present invention may also be used to modulate inflammation. For example, the polypeptide or polynucleotide may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic

shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or

5 IL-1.)

Hyperproliferative Disorders

A polypeptide or polynucleotide can be used to treat or detect hyperproliferative disorders, including neoplasms. A polypeptide or polynucleotide of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, a polypeptide or polynucleotide of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

20 Examples of hyperproliferative disorders that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but are not limited to neoplasms located in the: abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

25 Similarly, other hyperproliferative disorders can also be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

Infectious Disease

35 A polypeptide or polynucleotide of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases

may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, the polypeptide or polynucleotide of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

- 5 Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention. Examples of viruses, include, but are not limited to the following DNA and RNA viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Flaviviridae,
- 10 Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza), Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g.,
- 15 Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox , hemorrhagic fever, Measles, Mumps,
- 20 Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.

- Similarly, bacterial or fungal agents that can cause disease or symptoms and that
- 25 can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Nocardia), Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia, Brucellosis, Candidiasis, Campylobacter,
- 30 Coccidioidomycosis, Cryptococcosis, Dermatocytoses, Enterobacteriaceae (Klebsiella, Salmonella, Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Menigococcal), Pasteurellacea Infections (e.g., Actinobacillus, Haemophilus, Pasteurella), Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis,
- 35 and Staphylococcal. These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS

- related infections), paronychia, prostheses-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis, Chlamydia, Syphilis, Diphtheria, 5 Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or diseases.
- 10 Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide of the present invention include, but not limited to, the following families: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas.
- 15 These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), Malaria, pregnancy complications, and toxoplasmosis. A polypeptide or polynucleotide of the present invention can be used to treat or detect any of these symptoms or 20 diseases.
- 25 Preferably, treatment using a polypeptide or polynucleotide of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

- A polynucleotide or polypeptide of the present invention can be used to 30 differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion 35 injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal

or cardiac), vascular (including vascular endothelium), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, a polynucleotide or polypeptide of the present invention may increase 5 regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. A polynucleotide or polypeptide of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue 10 regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using a 15 polynucleotide or polypeptide of the present invention to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, 20 Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotide or polypeptide of the present invention.

Chemotaxis

25 A polynucleotide or polypeptide of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular 30 trauma or abnormality.

A polynucleotide or polypeptide of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. 35 For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that a polynucleotide or polypeptide of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, a polynucleotide or polypeptide of the present invention could be used as an inhibitor of chemotaxis.

5

Binding Activity

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit 10 (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural 15 or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

20 Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed 25 polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results 30 in a signal generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule 35 activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

- 5 All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptide from suitably manipulated cells or tissues.
- 10 Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the invention, (b) assaying a biological activity , and (b) determining if a biological activity of the polypeptide has been altered.
- 15

Other Activities

20 A polypeptide or polynucleotide of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

25 A polypeptide or polynucleotide of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide or polynucleotide of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

30 A polypeptide or polynucleotide of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, caricadic rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

35 A polypeptide or polynucleotide of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

Other Preferred Embodiments

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type Culture Collection and given the ATCC Deposit Number shown in Table 1 for said cDNA Clone Identifier.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

25 A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

30 A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

35 A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method

comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

- 5 Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined
10 from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

- A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95%
15 identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

- 20 The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

- 25 Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous
30 nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

- 35 The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95%

identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide

comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone
5 identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

10 Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as
15 defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide
20 molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition
25 associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a
30 sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

35 In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

- Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.
- 5
- Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.
- 10
- Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.
- 15
- Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.
- 20
- Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.
- 25
- 30
- 35

Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase 5 the level of said protein activity in said individual.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

10

Examples

Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. 15 Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being isolated in the vector 20 "Lambda Zap," the corresponding deposited clone is in "pBluescript."

	<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited Plasmid</u>
	Lambda Zap	pBluescript (pBS)
	Uni-Zap XR	pBluescript (pBS)
	Zap Express	pBK
25	lafmid BA	plafmid BA
	pSport1	pSport1
	pCMVSport 2.0	pCMVSport 2.0
	pCMVSport 3.0	pCMVSport 3.0
	pCR®2.1	pCR®2.1
30	Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are 35 commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1	

Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.

- Vectors pSport1, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain
- 10 DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed
- 15 into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

20 The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises

25 a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly

30 isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P - γ -ATP using T4 polynucleotide

35 kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982).)

The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 µl of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM MgCl₂, 0.01% (w/v) gelatin, 20 µM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then 5 be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA 10 synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

15

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR 20 using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

Example 3: Tissue Distribution of Polypeptide

Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, 25 among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P³² using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is 30 then used to examine various human tissues for mRNA expression.

Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are 35 mounted and exposed to film at -70°C overnight, and the films developed according to standard procedures.

Example 4: Chromosomal Mapping of the Polynucleotides

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This 5 primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on 10 either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

15 A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product 20 into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

25 The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are 30 identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The 35 cells are grown to an optical density 600 (O.D.⁶⁰⁰) of between 0.4 and 0.6. IPTG

(Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by 5 centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high 10 affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 15 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 20 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes 25 an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and 30 XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA

insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

5 The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

10 The following alternative method can be used to purify a polypeptide expressed in *E coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

15 Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

20 The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

25 The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

30 Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

 To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 µm membrane filter with appropriate surface area

- (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a
5 stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion
10 (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A₂₈₀
15 monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 µg of purified protein is loaded.

- 20 The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus

Expression System

- 25 In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient
30 polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak Drosophila promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that
35 express the cloned polynucleotide.

Many other baclovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baclovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baclovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.).

The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

Five μ g of a plasmid containing the polynucleotide is co-transfected with 1.0 μ g of a commercially available linearized baclovirus DNA ("BaculoGoldTM baclovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One μ g of BaculoGoldTM virus DNA and 5 μ g of the plasmid are mixed in a sterile well of a microtiter plate containing 50 μ l of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 μ l Lipofectin plus 90 μ l Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm

tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

- 5 After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture
10 and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.)
After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in
15 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

- To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection
20 ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 µCi of ³⁵S-methionine and 5 µCi ³⁵S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins
25 in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

30 **Example 8: Expression of a Polypeptide in Mammalian Cells**

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates

the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved
5 with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLV, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden),
10 pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSport 2.0, and pCMVSport 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

15 Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the
20 encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is
25 the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the
30 production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the
35 CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the

polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by 5 procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the vector does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a 10 heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and 15 purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for 20 transfection. Five μ g of the expression plasmid pC6 is cotransfected with 0.5 μ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are 25 trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of 30 methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μ M, 2 μ M, 5 μ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 μ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

35

Example 9: Protein Fusions

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; 5 Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having 10 more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

15 Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

20 For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not 25 be produced.

If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

30

Human IgG Fc region:

GGGATCCGGAGCCAAATCTTCTGACAAAATCACACATGCCAACCGTGCC
CAGCACCTGAATTCGAGGGTGCACCGTCAGTCTCCTCTCCCCCAAAACC
CAAGGACACCCTCATGATCTCCGGACTCCTGAGGTACATGCGTGGTGGT
35 GGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACG
GCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAAC
AGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTG

AATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAACCCCC
ATCGAGAAAACCATCTCCAAAGCCAAGGGCAGCCCCGAGAACCCACAGGT
GTACACCCTGCCCATCCCGGGATGAGCTGACCAAGAACCAAGGTAGCCT
GACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATGCCGTGGAGTGGGA
5 GAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCCTCCGTGCTGG
ACTCCGACGGCTCCTCTTCCTACAGCAAGCTCACCGTGGACAAGAGCA
GGTGGCAGCAGGGAACGTCTCTATGCTCCGTGATGCATGAGGCTCTGC
ACAACCACTACACGCAGAAGAGCCTCTCCGTCTCCGGTAAATGAGTGC
GACGGCCGCGACTCTAGAGGAT (SEQ ID NO:1)

10

Example 10: Production of an Antibody from a Polypeptide

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) For example, cells expressing a polypeptide of the present invention is administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of the secreted protein is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

In the most preferred method, the antibodies of the present invention are monoclonal antibodies (or protein binding fragments thereof). Such monoclonal antibodies can be prepared using hybridoma technology. (Köhler et al., *Nature* 256:495 (1975); Köhler et al., *Eur. J. Immunol.* 6:511 (1976); Köhler et al., *Eur. J. Immunol.* 6:292 (1976); Hammerling et al., in: *Monoclonal Antibodies and T-Cell Hybridomas*, Elsevier, N.Y., pp. 563-681 (1981).) In general, such procedures involve immunizing an animal (preferably a mouse) with polypeptide or, more preferably, with a secreted polypeptide-expressing cell. Such cells may be cultured in any suitable tissue culture medium; however, it is preferable to culture cells in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (*Gastroenterology* 80:225-232 (1981).) The hybridoma cells

obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide.

Alternatively, additional antibodies capable of binding to the polypeptide can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method
5 makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody
10 whose ability to bind to the protein-specific antibody can be blocked by the polypeptide. Such antibodies comprise anti-idiotypic antibodies to the protein-specific antibody and can be used to immunize an animal to induce formation of further protein-specific antibodies.

It will be appreciated that Fab and F(ab')2 and other fragments of the antibodies
15 of the present invention may be used according to the methods disclosed herein. Such fragments are typically produced by proteolytic cleavage, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). Alternatively, secreted protein-binding fragments can be produced through the application of recombinant DNA technology or through synthetic chemistry.

20 For in vivo use of antibodies in humans, it may be preferable to use "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric antibodies are known in the art. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214
25 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulian et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

30 **Example 11: Production Of Secreted Protein For High-Throughput Screening Assays**

The following protocol produces a supernatant containing a polypeptide to be tested. This supernatant can then be used in the Screening Assays described in Examples 13-20.

35 First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates)

- and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be
- 5 poly-lysine coated in advance for up to two weeks.
- Plate 293T cells (do not carry cells past P+20) at 2×10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.
- 10 The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8 or 9, into an appropriately labeled 96-well round bottom plate. With a
- 15 multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.
- 20 Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a12-channel pipetter with tips on every other channel,
- 25 adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37°C for 6 hours.
- While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or CHO-5 media (116.6 mg/L of CaCl₂ (anhyd); 0.00130 mg/L CuSO₄·5H₂O; 0.050 mg/L of Fe(NO₃)₃·9H₂O; 0.417 mg/L of FeSO₄·7H₂O; 311.80 mg/L of Kcl; 28.64 mg/L of MgCl₂; 48.84 mg/L of MgSO₄; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO₃; 62.50 mg/L of NaH₂PO₄·H₂O; 71.02 mg/L of Na₂HPO₄; .4320 mg/L of ZnSO₄·7H₂O; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-

Glucose; 130.85 mg/ml of L-Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H₂O; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H₂O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H₂O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H₂O; 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; and 0.680 mg/L of Vitamin B₁₂; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; and 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37°C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 13-20.

It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide directly (e.g., as a secreted protein) or by the polypeptide inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

5 GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in
10 many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

15 The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

20 The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and
25 (b) Class 2 includes IFN- α , IFN- γ , and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:2)).

30 Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS 35 elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

	<u>Ligand</u>	tyk2	<u>JAKs</u>			<u>STATs</u>	<u>GAS(elements) or ISRE</u>
			<u>Jak1</u>	<u>Jak2</u>	<u>Jak3</u>		
<u>IFN family</u>							
5	IFN-a/B	+	+	-	-	1,2,3	ISRE
	IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
	Il-10	+	?	?	-	1,3	
<u>gp130 family</u>							
10	IL-6 (Pleiotropic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
	Il-11(Pleiotropic)	?	+	?	?	1,3	
	OnM(Pleiotropic)	?	+	+	?	1,3	
	LIF(Pleiotropic)	?	+	+	?	1,3	
15	CNTF(Pleiotropic)	-/+	+	+	?	1,3	
	G-CSF(Pleiotropic)	?	+	?	?	1,3	
	IL-12(Pleiotropic)	+	-	+	+	1,3	
<u>g-C family</u>							
20	IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
	IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
	IL-7 (lymphocytes)	-	+	-	+	5	GAS
	IL-9 (lymphocytes)	-	+	-	+	5	GAS
	IL-13 (lymphocyte)	-	+	?	?	6	GAS
25	IL-15	?	+	?	+	5	GAS
<u>gp140 family</u>							
	IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
	IL-5 (myeloid)	-	-	+	-	5	GAS
30	GM-CSF (myeloid)	-	-	+	-	5	GAS
<u>Growth hormone family</u>							
	GH	?	-	+	-	5	
	PRL	?	+/-	+	-	1,3,5	
35	EPO	?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
<u>Receptor Tyrosine Kinases</u>							
	EGF	?	+	+	-	1,3	GAS (IRF1)
	PDGF	?	+	+	-	1,3	
40	CSF-1	?	+	+	-	1,3	GAS (not IRF1)

- To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 13-14, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., *Immunity* 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:
- 5':GCGCCTCGAGATTCCCCGAAATCTAGATTCCCCGAAATGATTCCCCG
10 AAATGATTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:3)
- The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)
- PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:
- 5':CTCGAGATTCCCCGAAATCTAGATTCCCCGAAATGATTCCCCGAAATG
20 ATTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCC
CTAACTCCGCCCATCCGCCCTAACTCCGCCAGTTCCGCCATTCTCCGC
CCCATGGCTGACTAATTTTTATTATGCAGAGGCCGAGGCCCTCGGC
CTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTGAGGCCAGGCTT
TGCAAAAGCTT:3' (SEQ ID NO:5)
- With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using Sall and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 13-14.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 15 and 16. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, Il-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 13: High-Throughput Screening Assay for T-cell Activity.

The following protocol is used to assess T-cell activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies)

with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

- During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1×10^7 cells in OPTI-MEM to T25 flask and incubate at 37°C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

- 5 The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Genticin, and 1% Pen-Strep. These cells are treated with supernatants containing a polypeptide as produced by the protocol described in Example 11.

- 10 On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

- 15 Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

- 20 After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

- 25 The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20°C until SEAP assays are performed according to Example 17. The plates containing the remaining treated cells are placed at 4°C and serve as a source of material for repeating the assay on a specific well if desired.

- 30 As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

- 35 **Example 14: High-Throughput Screening Assay Identifying Myeloid Activity**

The following protocol is used to assess myeloid activity by identifying factors, such as growth factors and cytokines, that may proliferate or differentiate myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 12. Thus, factors that increase SEAP activity indicate the ability to activate the Jak-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

To transiently transfet U937 cells with the GAS/SEAP/Neo construct produced in Example 12, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest 2×10^7 U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM Na₂HPO₄.7H₂O, 1 mM MgCl₂, and 675 uM CaCl₂. Incubate at 37°C for 45 min.

Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37°C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

These cells are tested by harvesting 1×10^8 cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of 5×10^5 cells/ml. Plate 200 ul cells per well in the 96-well plate (or 1×10^5 cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example 11. Incubate at 37°C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 17.

Example 15: High-Throughput Screening Assay Identifying Neuronal Activity.

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon

activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells can be assessed.

10 The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCGG -3' (SEQ ID NO:6)
5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:7)

15 Using the GAS:SEAP/Neo vector produced in Example 12, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

20 To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

25 PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

30 Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 11. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

35 To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS

(Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

- The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count
5 the cell number and add more low serum medium to reach final cell density as 5×10^5 cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to 1×10^5 cells/well). Add 50 ul supernatant produced by Example 11, 37°C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR
10 can be used, such as 50 ng/ml of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 17.

Example 16: High-Throughput Screening Assay for T-cell Activity

15 NF- κ B (Nuclear Factor κ B) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF- κ B regulates the expression of genes involved in immune cell activation, control of apoptosis (NF-
20 κ B appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- κ B is retained in the cytoplasm with I- κ B (Inhibitor κ B). However, upon stimulation, I- κ B is phosphorylated and degraded, causing NF- κ B to shuttle to the nucleus, thereby activating transcription of target
25 genes. Target genes activated by NF- κ B include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF- κ B promoter element are used to screen the supernatants produced in Example 11. Activators or inhibitors of NF- κ B would be useful in treating
30 diseases. For example, inhibitors of NF- κ B could be used to treat those diseases related to the acute or chronic activation of NF- κ B, such as rheumatoid arthritis.

- To construct a vector containing the NF- κ B promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF- κ B binding site (GGGGACTTTCCC) (SEQ ID NO:8), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:
- 5 5':GCGGCCTCGAGGGGACTTCCCGGGACTTCCGGGACTTCCGGGAC
TTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:9)
- The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:
- 5':GCGGCAAGCTTTGCAAAGCCTAGGC:3' (SEQ ID NO:4)
- 10 PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:
- 15 5':CTCGAGGGGACTTCCCGGGACTTCCGGGACTTCCGGGACTTCC
ATCTGCCATCTCAATTAGTCAGCAACCATACTCCGCCCTAACTCCGCCA
TCCCGCCCTAACTCCGCCAGTCCGCCATTCTCCGCCCATGGCTGACT
AATTTTTTATTATGCAGAGGCCGAGGCCGCTGGCCTTGAGCTATT
20 CAGAAGTAGTGAGGAGGCTTTTGAGGCCTAGGCTTTGCAAAAGCTT:
3' (SEQ ID NO:10)

Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF- κ B/SV40 fragment using XhoI and HindIII.

25 However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF- κ B/SV40/SEAP cassette is removed from the above NF- κ B/SEAP vector using restriction enzymes Sall and NotI, and inserted into a vector containing neomycin resistance. Particularly, the 30 NF- κ B/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with Sall and NotI.

Once NF- κ B/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 13. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described

in Example 13. As a positive control, exogenous TNF alpha (0.1,1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 17: Assay for SEAP Activity

- 5 As a reporter molecule for the assays described in Examples 13-16, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.
- 10 Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 µl of 2.5x dilution buffer into Optiplates containing 35 µl of a supernatant. Seal the plates with a plastic sealer and incubate at 65°C for 30 min. Separate the Optiplates to avoid uneven heating.
- 15 Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 µl Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 µl Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.
- 20 Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25
20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25

28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 18: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-3, used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO₂ incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-3 is made in 10% pluronic acid DMSO. To load the cells with fluo-3, 50 ul of 12 ug/ml fluo-3 is added to each well. The plate is

incubated at 37°C in a CO₂ incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

- For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10⁶ cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-3 solution in 10% pluronic acid DMSO is added to each ml of cell suspension.
- 5 The tube is then placed in a 37°C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10⁶ cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley CellWash with 200 ul, followed by an aspiration step to 100 ul final volume.
- 10 For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-3. The supernatant is added to the well, and a change in fluorescence is detected.
- To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and
- 15 (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event which has resulted in an increase in the intracellular Ca⁺⁺ concentration.

Example 19: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity

20

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In

25 addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the

30 cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

35 Because of the wide range of known factors capable of stimulating tyrosine kinase activity, the identification of novel human secreted proteins capable of activating

tyrosine kinase signal transduction pathways are of interest. Therefore, the following protocol is designed to identify those novel human secreted proteins capable of activating the tyrosine kinase signal transduction pathways.

- Seed target cells (e.g., primary keratinocytes) at a density of approximately 5 25,000 cells per well in a 96 well Loprodynne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4°C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are 15 used to cover the Loprodynne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

- To prepare extracts, A431 cells are seeded onto the nylon membranes of 20 Loprodynne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 11, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na₃VO₄, 2 mM Na₄P₂O₇) and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 25 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and 30 centrifuged for 15 minutes at 4°C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

- Generally, the tyrosine kinase activity of a supernatant is evaluated by 35 determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and

PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

- The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg₂₊ (5mM 5 ATP/50mM MgCl₂), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl₂, 5 mM MnCl₂, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30°C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.
- 10 The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mm EDTA and place the reactions on ice.
- Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37°C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide.
- 15 Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37°C for one hour. Wash the well as above.
- Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and 20 incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.
- 25 **Example 20: High-Throughput Screening Assay Identifying Phosphorylation Activity**
- As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 19, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be 30 used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by 35 substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1
5 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4°C until use.

10 A431 cells are seeded at 20,000/well in a 96-well Loprodyn filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 11 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

15 After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with
20 Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation.

**Example 21: Method of Determining Alterations in a Gene
25 Corresponding to a Polynucleotide**

RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in
30 SEQ ID NO:X. Suggested PCR conditions consist of 35 cycles at 95°C for 30 seconds; 60-120 seconds at 52-58°C; and 60-120 seconds at 70°C, using buffer solutions described in Sidransky, D., et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTHERM Polymerase. (Epicentre Technologies).
35 The intron-exon borders of selected exons is also determined and genomic PCR

products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton, T.A. and Graham, M.W., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 5 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenin-deoxy-uridine 5'-triphosphate (Boehringer Manheim), and FISH performed as described in Johnson, Cg. et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson, Cv. et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and 20 chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

25

Example 22: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is 30 a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with 35 specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10.

The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

5 The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

10 Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

15 Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

Example 23: Formulating a Polypeptide

20 The secreted polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

25 As a general proposition, the total pharmaceutically effective amount of secreted polypeptide administered parenterally per dose will be in the range of about 1 µg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If 30 given continuously, the secreted polypeptide is typically administered at a dose rate of about 1 µg/kg/hour to about 50 µg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending 35 on the desired effect.

Pharmaceutical compositions containing the secreted protein of the invention are administered orally, rectally, parenterally, intracistemally, intravaginally,

intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

- The secreted polypeptide is also suitably administered by sustained-release systems. Suitable examples of sustained-release compositions include semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules.
- 5 10 15 20 25 30
- Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman, U. et al., Biopolymers 22:547-556 (1983)), poly (2-hydroxyethyl methacrylate) (R. Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and R. Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D-(-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. USA 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

For parenteral administration, in one embodiment, the secreted polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

- The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as
- 5 ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose,
- 10 manose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

The secreted polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of

15 about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed

20 into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials

25 are filled with 5 ml of sterile-filtered 1% (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical

30 compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

35

Example 24: Method of Treating Decreased Levels of the Polypeptide

It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a secreted protein in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted form. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 23.

Example 25: Method of Treating Increased Levels of the Polypeptide

Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 23.

Example 26: Method of Treatment Using Gene Therapy

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

5 The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the
10 presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

15 The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

20 Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media
25 from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

30 The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 27: Method of Treatment Using Gene Therapy - In Vivo

Another aspect of the present invention is using *in vivo* gene therapy
35 methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression

of the polypeptide of the present invention. A polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the encoded polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, 5 see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata H. et al. (1997) *Cardiovasc. Res.* 35(3):470-479, Chao J et al. (1997) *Pharmacol. Res.* 35(6):517-522, Wolff J.A. (1997) *Neuromuscul. Disord.* 7(5):314-318, Schwartz B. et al. (1996) *Gene Ther.* 3(5):405-411, Tsurumi Y. et al. (1996) *Circulation* 94(12):3281-3290 10 (incorporated herein by reference).

The polynucleotide constructs of the present invention may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). These polynucleotide constructs can be delivered in a 15 pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the 20 polynucleotides may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) *Ann. NY Acad. Sci.* 772:126-139 and Abdallah B. et al. (1995) *Biol. Cell* 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs of the present invention used in 25 the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the 30 transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct of the present invention can be delivered to 35 the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial

- space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is
- 5 similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated,
- 10 although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of

15 DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of

20 nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for

25 delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding

30 for the polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

35 Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The

template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel
5 clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from
10 different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be used to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA of the present invention.

15 It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of each document cited (including patents, patent
20 applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference.

Further, the Sequence Listing submitted herewith in paper and computer readable forms are herein incorporated by reference in their entireties.

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>79</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (<i>including postal code and country</i>) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit July 3, 1997	Accession Number 209138
C. ADDITIONAL INDICATIONS (<i>leave blank if not applicable</i>) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (<i>if the indications are not for all designated States</i>)	
E. SEPARATE FURNISHING OF INDICATIONS (<i>leave blank if not applicable</i>) The indications listed below will be submitted to the International Bureau later (<i>specify the general nature of the indications, e.g., "Accession Number of Deposit"</i>)	

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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>80</u> , line <u>N/A</u>	
B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution American Type Culture Collection	
Address of depositary institution (<i>including postal code and country</i>) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America	
Date of deposit July 3, 1997	Accession Number 209139
C. ADDITIONAL INDICATIONS (<i>leave blank if not applicable</i>) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (<i>if the indications are not for all designated States</i>)	
E. SEPARATE FURNISHING OF INDICATIONS (<i>leave blank if not applicable</i>) The indications listed below will be submitted to the International Bureau later (<i>specify the general nature of the indications, e.g., "Accession Number of Deposit"</i>)	
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description
on page 82, line N/A

B. IDENTIFICATION OF DEPOSIT

Further deposits are identified on an additional sheet

Name of depositary institution

American Type Culture Collection

Address of depositary institution (*including postal code and country*)10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit July 9, 1997

Accession Number 209141

C. ADDITIONAL INDICATIONS (*leave blank if not applicable*) This information is continued on an additional sheetD. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (*if the indications are not for all designated States*)E. SEPARATE FURNISHING OF INDICATIONS (*leave blank if not applicable*)The indications listed below will be submitted to the International Bureau later (*specify the general nature of the indications, e.g., "Accession Number of Deposit"*)

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What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:
 - 5 (a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
 - (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
 - (c) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
 - 10 (d) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X;
 - (e) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X, having biological activity;
 - 15 (f) a polynucleotide which is a variant of SEQ ID NO:X;
 - (g) a polynucleotide which is an allelic variant of SEQ ID NO:X;
 - (h) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;
 - (i) a polynucleotide capable of hybridizing under stringent conditions to any 20 one of the polynucleotides specified in (a)-(h), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.
- 25 2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a secreted protein.
- 30 3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included 35 in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in ATCC Deposit No:Z, which is hybridizable to SEQ ID NO:X.

5

5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

10

6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

15

7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

20

9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.

25

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(b) a polypeptide fragment of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z, having biological activity;

30

(c) a polypeptide domain of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(d) a polypeptide epitope of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

(e) a secreted form of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

35

(f) a full length protein of SEQ ID NO:Y or the encoded sequence included in ATCC Deposit No:Z;

- (g) a variant of SEQ ID NO:Y;
- (h) an allelic variant of SEQ ID NO:Y; or
- (i) a species homologue of the SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, wherein the secreted form or the
5 full length protein comprises sequential amino acid deletions from either the C-terminus
or the N-terminus.

13. An isolated antibody that binds specifically to the isolated polypeptide of
claim 11.

10 14. A recombinant host cell that expresses the isolated polypeptide of claim
11.

15 15. A method of making an isolated polypeptide comprising:
(a) culturing the recombinant host cell of claim 14 under conditions such that
said polypeptide is expressed; and
(b) recovering said polypeptide.

20 16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition,
comprising administering to a mammalian subject a therapeutically effective amount of
the polypeptide of claim 11 or the polynucleotide of claim 1.

25 18. A method of diagnosing a pathological condition or a susceptibility to a
pathological condition in a subject comprising:
(a) determining the presence or absence of a mutation in the polynucleotide of
claim 1; and
(b) diagnosing a pathological condition or a susceptibility to a pathological
30 condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a
pathological condition in a subject comprising:
(a) determining the presence or amount of expression of the polypeptide of
35 claim 11 in a biological sample; and
(b) diagnosing a pathological condition or a susceptibility to a pathological
condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

- (a) contacting the polypeptide of claim 11 with a binding partner; and
- 5 (b) determining whether the binding partner effects an activity of the polypeptide.

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.

10 22. A method of identifying an activity in a biological assay, wherein the method comprises:

- (a) expressing SEQ ID NO:X in a cell;
- (b) isolating the supernatant;
- (c) detecting an activity in a biological assay; and
- 15 (d) identifying the protein in the supernatant having the activity.

23. The product produced by the method of claim 22.

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Gly Val Ile Phe Xaa
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20 25 30

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 35 40 45

5 Ser Ile Glu Leu His Ala Cys Gly Pro Tyr Pro Lys Pro Gly Leu Leu
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10 Ile Leu Leu Ala Pro Leu Ala Leu Trp Pro Ile Leu Leu Xaa
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35 Ser Ala Gly Pro Ala Xaa
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35 40 45

Gly Thr Leu Ser Ser Gln Xaa
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<210> 92

<211> 51

<212> PRT

50 <213> Homo sapiens

<220>

<221> SITE

<222> (51)

55 <223> Xaa equals stop translation

<400> 92

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			15
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	20	25	30
	Ser Tyr Cys Tyr Ile Leu Lys Val Pro Leu Arg Pro Lys Pro Leu Trp		
	35	40	45
30	Gln Leu Ser Asn Glu Ser Ile Cys Ser Glu Tyr Arg Val Glu Gly Gly		
	50	55	60
	Gln Gly His Gln Glu Leu Arg Met Phe Leu Arg Leu Met Arg Pro Arg		
	65	70	75
			80
35	Tyr Trp Val His Gly Gly Pro Arg Ser Leu Cys Asp Ser Cys Ser Leu		
	85	90	95
40	Leu Pro Pro Cys Leu Asp Pro Ala Ser Ala Gln Lys Ala Asn Ser Leu		
	100	105	110
	Asp Ser Lys Gly Leu Pro Arg Pro Ile Ser Met Ser Cys Ser Cys Gln		
	115	120	125
45	Leu Pro Val Pro Ser Leu Asp Leu Ser Ser Cys Leu Ala Pro Ser Leu		
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	Pro Thr Pro His Ile Phe Thr Asn Lys Arg Lys Xaa		
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60	<223> Xaa equals stop translation		

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 10 35 40 45
 Ile Ser Asp His Ile Leu Val Leu Leu Lys Thr Phe Xaa
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 25
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 Met Trp Phe Glu Ile Leu Pro Gly Leu Ser Val Met Gly Val Cys Leu
 1 5 10 15
 30 Leu Ile Pro Gly Leu Ala Thr Ala Tyr Ile His Arg Phe Thr Asn Gly
 20 25 30
 Gly Lys Glu Lys Arg Val Ala His Phe Gly Tyr His Trp Ser Leu Met
 35 40 45
 35 Glu Arg Asp Arg Arg Ile Ser Gly Val Asp Arg Tyr Tyr Val Ser Lys
 50 55 60
 40 Gly Leu Glu Asn Ile Asp Xaa
 65 70
 45
 <210> 96
 <211> 37
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SITE
 <222> (37)
 <223> Xaa equals stop translation
 50
 <400> 96
 Met Val Phe Leu Leu Leu Leu Phe Gly Phe Phe Asp Gly Ser
 55 1 5 10 15
 Leu Arg Ser Pro Leu Leu Ile Ile His Leu Gly Pro Ala Pro Thr
 20 25 30
 60 Phe Leu Gln Ile Xaa

35

5 <210> 97
 <211> 60
 <212> PRT
 <213> Homo sapiens

10 <220>
 10 <221> SITE
 <222> (60)
 <223> Xaa equals stop translation

15 <400> 97
 15 Met Leu Cys Gln Thr Ile Pro Leu Cys Asn Arg Leu His Ile Val Phe
 1 5 10 15

20 Met Ile Leu Ile Lys Leu Tyr Val Glu Thr Glu Cys Glu Val Lys Ser
 20 25 30

20 Glu His Lys Lys Ile Met His Asp Glu Ile Ala Tyr His Phe Ile Gly
 35 40 45

25 Tyr Leu Leu Cys Ile Tyr Thr Leu Arg Pro Leu Xaa
 50 55 60

30 <210> 98
 30 <211> 44
 <212> PRT
 <213> Homo sapiens

35 <220>
 35 <221> SITE
 <222> (44)
 <223> Xaa equals stop translation

40 <400> 98
 40 Met Ser Val Ser Ser Asn Leu Trp Gln Thr Leu Ile Leu Leu Ser
 1 5 10 15

45 Leu Trp Phe Cys Leu Phe Pro Glu Cys His Ile Val Gly Ile Ile Gln
 20 25 30

45 Leu Cys Arg Leu Phe Arg Leu Pro Ser Phe Thr Xaa
 35 40

50 <210> 99
 50 <211> 32
 <212> PRT
 <213> Homo sapiens

55 <220>
 55 <221> SITE
 <222> (32)
 <223> Xaa equals stop translation

60 <400> 99
 60 Met Cys Cys Arg Ala Gly Gly Ser Gln Ser Pro Gln Val Met Val Val

1	5	10	15	
Leu Ile Ile Ile Leu Gly Pro Trp Gly Gly Val Arg Ile Asp Ala Xaa				
	20	25	30	
5				
<210> 100 <211> 180 <212> PRT <213> Homo sapiens				
10 <210> 100 <211> 180 <212> PRT <213> Homo sapiens				
15 <400> 100 Met Tyr Ser Cys Leu Leu Leu Pro Asp Leu Leu Tyr Leu Thr Leu Ser 1 5 10 15				
20 Pro Leu Val Val Ala Met Leu Leu Thr Pro His Phe Asn Val Ala Asn 20 25 30				
Pro Gln Asn Leu Leu Ala Gly Leu Trp Leu Glu Asn Glu His Ser Phe 35 40 45				
25 Thr Leu Met Ala Pro Glu Arg Ala Arg Thr His His Cys Gln Pro Glu 50 55 60				
Glu Arg Lys Val Leu Phe Cys Leu Phe Pro Ile Val Pro Asn Ser Gln 65 70 75 80				
30 Ala Gln Val Gln Pro Pro Gln Met Pro Pro Phe Cys Cys Ala Ala Ala 85 90 95				
35 Lys Glu Lys Thr Gln Glu Glu Gln Leu Gln Glu Pro Leu Gly Ser Gln 100 105 110				
Cys Pro Asp Thr Cys Pro Asn Ser Leu Cys Pro Ser His Thr Gln Leu 115 120 125				
40 Thr Lys Ala Asn Thr Leu Ser Leu Phe Phe Phe Ser Phe Phe Leu 130 135 140				
45 Ser Arg Val Ser Leu Leu Ser Pro Arg Leu Glu Cys Asn Gly Arg Ile 145 150 155 160				
Leu Ala His Cys Asn Leu His Leu Pro Gly Ser Ser Asn Ser Pro Val 165 170 175				
50 Ser Ala Ser Arg 180				
55 <210> 101 <211> 212 <212> PRT <213> Homo sapiens				
60 <220> <221> SITE <222> (45)				

<223> Xaa equals any one of the naturally occurring L-amino acids

<220>

<221> SITE

5 <222> (195)

<223> Xaa equals any one of the naturally occurring L-amino acids

<220>

<221> SITE

10 <222> (212)

<223> Xaa equals stop translation

<400> 101

Met Arg Leu Phe Leu Trp Asn Ala Val Leu Thr Leu Phe Val Thr Ser
1 5 10 15

Leu Ile Gly Ala Leu Ile Pro Glu Pro Glu Val Lys Ile Glu Val Leu
20 25 30

20 Gln Lys Pro Phe Ile Cys His Arg Lys Thr Lys Gly Xaa Asp Leu Met
35 40 45

Leu Val His Tyr Glu Gly Tyr Leu Glu Lys Asp Gly Ser Leu Phe His
50 55 60

25 Ser Thr His Lys His Asn Asn Gly Gln Pro Ile Trp Phe Thr Leu Gly
65 70 75 80

30 Ile Leu Glu Ala Leu Lys Gly Trp Asp Gln Gly Leu Lys Gly Met Cys
85 90 95

Val Gly Glu Lys Arg Lys Leu Ile Ile Pro Pro Ala Leu Gly Tyr Gly
100 105 110

35 Lys Glu Gly Lys Gly Lys Ile Pro Pro Glu Ser Thr Leu Ile Phe Asn
115 120 125

Ile Asp Leu Leu Glu Ile Arg Asn Gly Pro Arg Ser His Glu Ser Phe
130 135 140

40 Gln Glu Met Asp Leu Asn Asp Asp Trp Lys Leu Ser Lys Asp Glu Val
145 150 155 160

45 Lys Ala Tyr Leu Lys Lys Glu Phe Glu Lys His Gly Ala Val Val Asn
165 170 175

Glu Ser His His Asp Ala Leu Val Glu Asp Ile Phe Asp Lys Glu Asp
180 185 190

50 Glu Asp Xaa Tyr Gly Phe Ile Ser Ala Arg Glu Phe Thr Tyr Lys His
195 200 205

Asp Glu Leu Xaa
210

55

<210> 102

<211> 621

<212> PRT

60 <213> Homo sapiens

<220>
 <221> SITE
 <222> (137)
 5 <223> Xaa equals any one of the naturally occurring L-amino acids

 <400> 102
 Met Gly Leu Leu Ser Asp Pro Val Arg Arg Arg Ala Leu Ala Arg Leu
 1 5 10 15
 10 Val Leu Arg Leu Asn Ala Pro Leu Cys Val Leu Ser Tyr Val Ala Gly
 20 25 30

 Ile Ala Trp Phe Leu Ala Leu Val Phe Pro Pro Leu Thr Gln Arg Thr
 15 35 40 45

 Tyr Met Ser Glu Asn Ala Met Gly Ser Thr Met Val Glu Glu Gln Phe
 50 55 60

 20 Ala Gly Gly Asp Arg Ala Arg Ala Phe Ala Arg Asp Phe Ala Ala His
 65 70 75 80

 Arg Lys Lys Ser Gly Ala Leu Pro Val Ala Trp Leu Glu Arg Thr Met
 85 90 95
 25 Arg Ser Val Gly Leu Glu Val Tyr Thr Gln Ser Phe Ser Arg Lys Leu
 100 105 110

 Pro Phe Pro Asp Glu Thr His Glu Arg Tyr Met Val Ser Gly Thr Asn
 30 115 120 125

 Val Tyr Gly Ile Leu Arg Ala Pro Xaa Ala Ala Ser Thr Glu Ser Leu
 130 135 140

 35 Val Leu Thr Val Pro Cys Gly Ser Asp Ser Thr Asn Ser Gln Ala Val
 145 150 155 160

 Gly Leu Leu Leu Ala Leu Ala Ala His Phe Arg Gly Gln Ile Tyr Trp
 165 170 175
 40 Ala Lys Asp Ile Val Phe Leu Val Thr Glu His Asp Leu Leu Gly Thr
 180 185 190

 45 Glu Ala Trp Leu Glu Ala Tyr His Asp Val Asn Val Thr Gly Met Gln
 195 200 205

 Ser Ser Pro Leu Gln Gly Arg Ala Gly Ala Ile Gln Ala Ala Val Ala
 210 215 220

 50 Leu Glu Leu Ser Ser Asp Val Val Thr Ser Leu Asp Val Ala Val Glu
 225 230 235 240

 Gly Leu Asn Gly Gln Leu Pro Asn Leu Asp Leu Leu Asn Leu Phe Gln
 245 250 255
 55 Thr Phe Cys Gln Lys Gly Gly Leu Leu Cys Thr Leu Gln Gly Lys Leu
 260 265 270

 60 Gln Pro Glu Asp Trp Thr Ser Leu Asp Gly Pro Leu Gln Gly Leu Gln
 275 280 285

Thr Leu Leu Leu Met Val Leu Arg Gln Ala Ser Gly Arg Pro His Gly
 290 295 300

 5 Ser His Gly Leu Phe Leu Arg Tyr Arg Val Glu Ala Leu Thr Leu Arg
 305 310 315 320

 Gly Ile Asn Ser Phe Arg Gln Tyr Lys Tyr Asp Leu Val Ala Val Gly
 325 330 335

 10 Lys Ala Leu Glu Gly Met Phe Arg Lys Leu Asn His Leu Leu Glu Arg
 340 345 350

 15 Leu His Gln Ser Phe Phe Leu Tyr Leu Leu Pro Gly Leu Ser Arg Phe
 355 360 365

 Val Ser Ile Gly Leu Tyr Met Pro Ala Val Gly Phe Leu Leu Val
 370 375 380

 20 Leu Gly Leu Lys Ala Leu Glu Leu Trp Met Gln Leu His Glu Ala Gly
 385 390 395 400

 Met Gly Leu Glu Glu Pro Gly Gly Ala Pro Gly Pro Ser Val Pro Leu
 405 410 415

 25 Pro Pro Ser Gln Gly Val Gly Leu Ala Ser Leu Val Ala Pro Leu Leu
 420 425 430

 Ile Ser Gln Ala Met Gly Leu Ala Leu Tyr Val Leu Pro Val Leu Gly
 30 435 440 445

 Gln His Val Ala Thr Gln His Phe Pro Val Ala Glu Ala Glu Ala Val
 450 455 460

 35 Val Leu Thr Leu Leu Ala Ile Tyr Ala Ala Gly Leu Ala Leu Pro His
 465 470 475 480

 Asn Thr His Arg Val Val Ser Thr Gln Ala Pro Asp Arg Gly Trp Met
 485 490 495

 40 Ala Leu Lys Leu Val Ala Leu Ile Tyr Leu Ala Leu Gln Leu Gly Cys
 500 505 510

 Ile Ala Leu Thr Asn Phe Ser Leu Gly Phe Leu Leu Ala Thr Thr Met
 45 515 520 525

 Val Pro Thr Ala Ala Leu Ala Lys Pro His Gly Pro Arg Thr Leu Tyr
 530 535 540

 50 Ala Ala Leu Leu Val Leu Thr Ser Pro Ala Ala Thr Leu Leu Gly Ser
 545 550 555 560

 Leu Phe Leu Trp Arg Glu Leu Gln Glu Ala Pro Leu Ser Leu Ala Glu
 565 570 575

 55 Gly Trp Gln Leu Phe Leu Ala Ala Leu Ala Gln Gly Val Leu Glu His
 580 585 590

 His Thr Tyr Gly Ala Leu Leu Phe Pro Leu Leu Ser Leu Gly Leu Tyr
 60 595 600 605

Pro Cys Trp Leu Leu Phe Trp Asn Val Leu Phe Trp Lys
 610 615 620

5 <210> 103
 <211> 287
 <212> PRT
 <213> Homo sapiens

10 <220>
 <221> SITE
 <222> (263)
 <223> Xaa equals any one of the naturally occurring L-amino acids

15 <400> 103
 Met Ala Leu Leu Pro Ile Phe Phe Gly Ala Leu Arg Ser Val Arg Cys
 1 5 10 15

20 Ala Arg Gly Lys Asn Ala Ser Asp Met Pro Glu Thr Ile Thr Ser Arg
 20 25 30

Asp Ala Ala Arg Phe Pro Ile Ile Ala Ser Cys Thr Leu Leu Gly Leu
 35 40 45

25 Tyr Leu Phe Phe Lys Ile Phe Ser Gln Glu Tyr Ile Asn Leu Leu Leu
 50 55 60

30 Ser Met Tyr Phe Phe Val Leu Gly Ile Leu Ala Leu Ser His Thr Ile
 65 70 75 80

Ser Pro Phe Met Asn Lys Phe Phe Pro Ala Ser Phe Pro Asn Arg Gln
 85 90 95

35 Tyr Gln Leu Leu Phe Thr Gln Gly Ser Gly Glu Asn Lys Glu Glu Ile
 100 105 110

Ile Asn Tyr Glu Phe Asp Thr Lys Asp Leu Val Cys Leu Gly Leu Ser
 115 120 125

40 Ser Ile Val Gly Val Trp Tyr Leu Leu Arg Lys His Trp Ile Ala Asn
 130 135 140

45 Asn Leu Phe Gly Leu Ala Phe Ser Leu Asn Gly Val Glu Leu Leu His
 145 150 155 160

Leu Asn Asn Val Ser Thr Gly Cys Ile Leu Leu Gly Gly Leu Phe Ile
 165 170 175

50 Tyr Asp Val Phe Trp Val Phe Gly Thr Asn Val Met Val Thr Val Ala
 180 185 190

Lys Ser Phe Glu Ala Pro Ile Lys Leu Val Phe Pro Gln Asp Leu Leu
 195 200 205

55 Glu Lys Gly Leu Glu Ala Asn Asn Phe Ala Met Leu Gly Leu Gly Asp
 210 215 220

60 Val Val Ile Pro Gly Ile Phe Ile Ala Leu Leu Leu Arg Phe Asp Ile
 225 230 235 240

Ser Leu Lys Lys Asn Thr His Thr Tyr Phe Tyr Thr Ser Phe Ala Ala
 245 250 255

5 Tyr Ile Phe Gly Leu Gly Xaa Tyr His Leu His His Ala His Leu Gln
 260 265 270

Ala Cys Ser Val Met Arg Ser Gln Ile Leu Arg Ile Gln Arg Gln
 275 280 285

10

<210> 104
 <211> 32
 <212> PRT
 15 <213> Homo sapiens

<220>
 <221> SITE
 <222> (32)
 20 <223> Xaa equals stop translation

<400> 104
 Met Ser Arg Leu Leu Leu Phe Gly Arg Leu Cys Ser Leu Trp Cys
 1 5 10 15

25 Leu Ser Trp Leu Tyr Ser Thr Asp Thr Arg Pro Leu Leu Arg Gly Xaa
 20 25 30

30

<210> 105
 <211> 77
 35 <212> PRT
 <213> Homo sapiens

<400> 105
 Met Leu Pro Arg Leu Val Leu Asn Ser Trp Ala Cys Pro Pro Gln Pro
 40 1 5 10 15

Pro Lys Val Leu Glu Leu Gln Ala Cys Ala Thr Ile Ser Ser Leu Ile
 20 25 30

45 Thr Leu Phe Leu Met Phe Ile Lys Ser Ser His Pro Leu Ser Leu Ala
 35 40 45

Glu Ala Ser Gln Glu Gly Gln Asn Gln Leu Gln Ser Thr Ile Ser Asp
 50 55 60

50 Pro Glu Thr Trp Ile Leu Phe Val His Leu Asn Val Thr
 65 70 75

55 <210> 106
 <211> 45
 <212> PRT
 <213> Homo sapiens

60 <220>

<221> SITE
 <222> (45)
 <223> Xaa equals stop translation

5 <400> 106
 Met Val Phe Leu Val Phe Tyr Val Leu Arg Ala Leu Lys Cys Asn Ser
 1 5 10 15

10 Ser Tyr His Ser Cys Thr Asn Val Leu Thr Gln Ile Ala Ser Gln Ile
 20 25 30

Asp Lys Thr Leu Asn Asn Phe Ser Leu Lys Lys Cys Xaa
 35 40 45

15 <210> 107
 <211> 42
 <212> PRT
 <213> Homo sapiens

20 <220>
 <221> SITE
 <222> (42)
 <223> Xaa equals stop translation

25 <400> 107
 Met Asn Pro Cys Leu Ser Ile Ile Phe Leu Leu Thr Pro Val Leu Leu
 1 5 10 15

30 Ser His Pro Leu Gln Ser Leu His Phe Leu Leu Lys Val Asp Leu Asp
 20 25 30

Phe Ser Leu Ser Cys Ser Ile Cys Thr Xaa
 35 40

35 <210> 108
 <211> 70
 <212> PRT
 <213> Homo sapiens

40 <220>
 <221> SITE
 <222> (70)
 <223> Xaa equals stop translation

45 <400> 108
 Met Thr Val Tyr Leu Leu Lys Thr His Pro Cys Phe Phe Val Ala Tyr
 1 5 10 15

50 Gln Met Gln Val Ala Leu Ile Ile Leu Leu Pro Gly Leu Arg Asn Ser
 20 25 30

55 Lys Thr Val Thr Met Pro Leu Ser Pro Ala Leu Leu Pro Thr Leu Leu
 35 40 45

Phe Phe Pro Ser Pro Thr Pro Phe Phe His Pro Phe Leu Ser Val Leu
 50 55 60

60 Cys Cys Phe Lys Tyr Xaa

65 70

5 <210> 109
<211> 49
<212> PRT
<213> Homo sapiens

10 <220>
<221> SITE
<222> (43)
<223> Xaa equals any one of the naturally occurring L-amino acids

15 <220>
<221> SITE
<222> (49)
<223> Xaa equals stop translation

20 <400> 109
Met His Ala Thr Cys Thr Arg Thr Trp Arg Ala Gln Val Ser Leu His
1 5 . 10 15

Gln Pro Pro Cys Ser Arg Asp Trp Lys Ile Cys His Leu Leu Val Val
20 25 30

25 Leu Ser Leu Pro Pro Pro Thr Pro Ala Arg Xaa Pro Glu Phe Leu Asn
35 40 45

30 Xaa

35 <210> 110
<211> 193
<212> PRT
<213> Homo sapiens

40 <220>
<221> SITE
<222> (193)
<223> Xaa equals stop translation

45 <400> 110
Met Ile Arg Asn Asp Gln Asp Ser Leu Met Gln Leu Leu Gln Leu Gly
1 5 10 15

Leu Val Val Leu Gly Ser Gln Glu Ser Gln Glu Ser Asp Leu Ser Lys
20 25 30

50 Gln Leu Ile Ser Val Ile Ile Gly Val Ala Leu Leu Leu Val
35 40 45

Leu Val Ile Met Thr Met Ala Phe Val Cys Val Arg Lys Ser Tyr Asn
50 55 60

55 Arg Lys Leu Gln Ala Met Lys Ala Ala Lys Glu Ala Arg Lys Thr Ala
65 70 75 80

60 Ala Gly Val Met Pro Ser Ala Pro Ala Ile Pro Gly Thr Asn Met Tyr
85 90 95

Asn Thr Glu Arg Ala Asn Pro Met Leu Asn Leu Pro Asn Lys Asp Leu
100 105 110

5 Gly Leu Glu Tyr Leu Ser Pro Ser Asn Asp Leu Asp Ser Val Ser Val
115 120 125

Asn Ser Leu Asp Asp Asn Ser Val Asp Val Asp Lys Asn Ser Gln Glu
130 135 140

10 Ile Lys Glu His Arg Pro Pro His Thr Pro Pro Glu Pro Asp Pro Glu
145 150 155 160

Pro Leu Ser Val Val Leu Leu Gly Arg Gln Ala Gly Ala Ser Gly Gln
15 165 170 175

Leu Glu Gly Pro Ser Tyr Thr Asn Ala Gly Leu Asp Thr Thr Asp Leu
180 185 190

20 Xaa

25 <210> 111
<211> 71
<212> PRT
<213> Homo sapiens

30 <220>
<221> SITE
<222> (64)
<223> Xaa equals any one of the naturally occurring L-amino acids

35 <400> 111
Met Ala His Val Val Val Ala Arg Asn Glu Cys Leu Ile Arg Ala Phe
1 5 10 15

Leu Phe Leu Leu His Cys Val Ser Leu Leu Pro Ser Pro Gly Glu Val
20 25 30

40 Asn Ile Arg His Thr Leu Phe Thr Val Glu Glu Arg Leu Thr Thr Pro
35 40 45

45 Arg Ala Leu Lys Leu Ser Leu Ser Leu Ile Val Ser Leu His Ala Xaa
50 55 60

Cys Arg Lys Gln Glu Cys Ser
65 70

50 <210> 112
<211> 36
<212> PRT
<213> Homo sapiens

55 <220>
<221> SITE
<222> (36)
<223> Xaa equals stop translation

60

<400> 112
Met Arg Leu Thr Glu Lys Asp Thr Val Leu Phe Thr Lys Gly Val Leu
1 5 10 15

5 Phe Leu His Leu Phe Ile Asn Ala Leu Phe Trp Tyr Cys Lys Phe Gly
20 25 30

His Asn Phe Xaa
35

10

<210> 113
<211> 60
<212> PRT
15 <213> Homo sapiens

<220>
<221> SITE
<222> (60)
20 <223> Xaa equals stop translation
-

<400> 113
Met Thr Ser Val Ser Thr Gln Leu Ser Leu Val Leu Met Ser Leu Leu
1 5 10 15

25 Leu Val Leu Pro Val Val Glu Ala Val Glu Ala Gly Asp Ala Ile Ala
20 25 30

Leu Leu Leu Gly Val Val Leu Ser Ile Thr Gly Ile Cys Ala Cys Leu
30 35 40 45

Gly Val Tyr Ala Arg Lys Arg Asn Gly Gln Met Xaa
50 55 60

35

<210> 114
<211> 29
<212> PRT
40 <213> Homo sapiens

<220>
<221> SITE
<222> (29)
45 <223> Xaa equals stop translation

<400> 114
Met Asn Ser Phe Trp Ser Lys Leu Leu Val Leu Pro Leu Leu Ala Pro
1 5 10 15

50 Leu Ser Met Ala Arg Ala Ser Ala Cys Gln Arg Trp Xaa
20 25

55 <210> 115
<211> 25
<212> PRT
<213> Homo sapiens

60 <220>
<221> SITE

<222> (25)
<223> Xaa equals stop translation

5 <400> 115
Met Met Arg Leu Leu Asp Leu Arg Ile Phe Leu Met Ile His His Lys
1 5 10 15

Ala Lys Ser Trp Glu Ser His Thr Xaa
20 25

10

<210> 116
<211> 35
<212> PRT
15 <213> Homo sapiens

<220>
<221> SITE
<222> (35)
20 <223> Xaa equals stop translation

<400> 116
Met Pro Leu Ser Leu Leu Ile Val Trp Lys Leu Glu Leu Cys Val
1 5 10 15

25 Gly Ser Ala Leu Val Leu Ile His Thr Gln Arg Arg Tyr Ile Ile Leu
20 25 30

30 Gln Val Xaa
35

<210> 117
<211> 78
35 <212> PRT
<213> Homo sapiens

<220>
<221> SITE
40 <222> (78)
<223> Xaa equals stop translation

<400> 117
Met Leu Leu Ala Thr Leu Leu Leu Leu Leu Gly Gly Ala Leu Ala
45 1 5 10 15

His Pro Asp Arg Ile Ile Phe Pro Asn His Ala Cys Glu Asp Pro Pro
20 25 30

50 Ala Val Leu Leu Glu Val Gln Gly Thr Leu Gln Arg Pro Leu Val Arg
35 40 45

Asp Ser Arg Thr Ser Pro Ala Asn Cys Thr Trp Leu Thr Lys Arg Val
55 50 55 60

55 Gln Gln Met Leu Leu Phe His Ser Tyr Gly Ile Ala Gln Xaa
65 70 75

60 <210> 118

<211> 44
 <212> PRT
 <213> Homo sapiens

5 <220>
 <221> SITE
 <222> (44)
 <223> Xaa equals stop translation

10 <400> 118
 Met Thr Gly Val Phe Lys Leu Pro Leu Leu Phe Trp Val His Glu Ala
 1 5 10 15

15 Ser Val Gly Gly Cys Pro Tyr Val Lys Leu Val Glu Phe Glu Glu Met
 20 25 30

Leu Thr Leu Tyr Gly Ile Leu Leu Ile Leu Phe Xaa
 35 40

20 <210> 119
 <211> 46
 <212> PRT
 <213> Homo sapiens

25 <220>
 <221> SITE
 <222> (46)
 <223> Xaa equals stop translation

30 <400> 119
 Met Gln Leu Ala Pro Phe Ile Ser Ile Pro Val Leu Ser Gly Thr Thr
 1 5 10 15

35 Pro Trp Thr Ala Val Phe Arg Ala Ser Ser Ile Cys Thr Pro Leu Leu
 20 25 30

Thr Leu Ser Ala Ala Gly Met Leu Val Glu Ser Ser Leu Xaa
 35 40 45

40 <210> 120
 <211> 29
 <212> PRT
 <213> Homo sapiens

45 <220>
 <221> SITE
 <222> (29)
 <223> Xaa equals stop translation

50 <400> 120
 Met Pro Pro Leu Ser Asp Ile Leu Leu Thr Val Ala Val Val Ala Phe
 1 5 10 15

55 Glu Met Thr Gly His Ile Tyr Ile Trp Pro His Thr Xaa
 20 25

60 <210> 121

<211> 62
 <212> PRT
 <213> Homo sapiens

5 <400> 121
 Met Glu Leu Pro Cys Asp Cys Ser Lys Leu Leu Tyr Cys Lys Phe Ser
 1 5 10 15

10 Val Trp His Leu Pro Val Asn Ala Met Lys Leu Leu Ile Ile Phe Leu
 20 25 30

Lys Val Leu His Cys Leu Phe Phe Leu Leu Cys Lys Phe Leu Tyr
 35 40 45

15 Thr Leu Ile Val Ile Leu Thr Asp Lys Tyr Ser Ile Leu Asn
 50 55 60

20 <210> 122
 <211> 87
 <212> PRT
 <213> Homo sapiens

25 <220>
 <221> SITE
 <222> (68)
 <223> Xaa equals any one of the naturally occurring L-amino acids

30 <220>
 <221> SITE
 <222> (72)
 <223> Xaa equals any one of the naturally occurring L-amino acids

35 <220>
 <221> SITE
 <222> (87)
 <223> Xaa equals stop translation

40 <400> 122
 Met Pro Val Ser Trp Gly Cys Pro Ser Lys Thr Pro Gln Thr Arg Ala
 1 5 10 15

Tyr Thr Arg Cys Val Tyr Phe Leu Met Val Leu Glu Ala Gly Val Gly
 20 25 30

45 Gly His Ser Val Ser Arg Val Gly Ser Leu Glu Val Pro Pro Trp Leu
 35 40 45

50 Val Ala Ala Asn Asn Phe Pro His Leu Met Trp Ser Ser Phe Cys Val
 50 55 60

Gly Pro His Xaa Val Phe Leu Xaa Asp Pro Ser Leu Pro Asp Pro Gly
 65 70 75 80

55 Pro Pro Asn Asn Leu Thr Xaa
 85

60 <210> 123
 <211> 64

<212> PRT
 <213> Homo sapiens

5 <220>
 <221> SITE
 <222> (64)
 <223> Xaa equals stop translation

10 <400> 123
 Met Cys Tyr Phe Leu Glu Ile Ser Leu Leu Met Val Phe Ala Leu Asn
 1 5 10 15

Ile Lys Ala Ala Tyr Gly Cys Cys Asn Ile Asn Gly Thr Glu Val His
 20 25 30

15 Arg Ala Lys Gly Pro Val Ser Val Pro Phe Pro Leu Ser Arg Pro Leu
 35 40 45

20 Ser Gly Thr Pro Leu Leu Asp Arg Leu Arg Pro Phe Gln Thr Leu Xaa
 50 55 60

25

<210> 124
 <211> 36
 <212> PRT
 <213> Homo sapiens

30 <220>
 <221> SITE
 <222> (36)
 <223> Xaa equals stop translation

35 <400> 124
 Met Pro Leu Pro Ser Ser Phe Pro Leu Pro Val Phe Leu Ser Ser Cys
 1 5 10 15

40 Pro Phe Leu Met Ser Val Ser Ile Gly Phe Leu Ile Leu Val Phe Asn
 20 25 30

Val His Pro Xaa
 35

45

<210> 125
 <211> 32
 <212> PRT
 <213> Homo sapiens

50 <220>
 <221> SITE
 <222> (32)
 <223> Xaa equals stop translation

55 <400> 125
 Met Phe Ile Phe Cys Val Ser Leu Ala Phe Leu Pro Arg Phe Ile Ser
 1 5 10 15

60

Pro Gln Ser Cys Glu Trp Ala Gly Leu Ser Leu Val Trp His His Xaa
20 25 30

5

10 <210> 126
<211> 41
<212> PRT
<213> Homo sapiens

15 <220>
<221> SITE
<222> (41)
<223> Xaa equals stop translation

20 <400> 126
Met Lys Asn Asn Thr Gln Lys Arg Leu Phe Leu Trp Gly Glu Leu Leu
1 5 10 15

Leu Gln Asp Leu Ala Leu Ile Leu Tyr Leu Ser Ile Phe Leu Lys Ser
20 25 30

25 Thr Leu Thr Asn Leu Asn Leu Phe Xaa
35 40

30 <210> 127
<211> 28
<212> PRT
<213> Homo sapiens

35 <220>
<221> SITE
<222> (28)
<223> Xaa equals stop translation

40 <400> 127
Met Leu Asn Val Phe Phe Ser Leu Ile Leu Phe Phe Ser Pro Asn Arg
1 5 10 15

Ala Leu Pro Ala Ile Ser Ser Cys Ile Thr Phe Xaa
20 25

45

50 <210> 128
<211> 69
<212> PRT
<213> Homo sapiens

55 <220>
<221> SITE
<222> (69)
<223> Xaa equals stop translation

60 <400> 128
Met Arg Ala Val Gly Glu Arg Leu Leu Lys Leu Gln Arg Leu Pro
1 5 10 15

Gln Ala Glu Pro Val Glu Ile Val Ala Phe Ser Val Ile Ile Leu Phe
 20 25 30

5 Thr Ala Thr Val Leu Leu Leu Leu Ile Ala Cys Ser Cys Cys Cys
 35 40 45

Thr His Cys Cys Cys Pro Glu Arg Arg Gly Arg Lys Val Gln Val Gln
 50 55 60

10 Pro Thr Pro Pro Xaa
 65

15 <210> 129
 <211> 87
 <212> PRT
 <213> Homo sapiens

20 <400> 129
 Met Asp Pro Arg Arg Val Thr Ala Cys Cys His Val Trp Thr Val Gly
 1 5 10 15

Leu Phe Cys Ile Trp Ala Val Gly Leu Ser Cys Ser Leu Ser Leu Ser
 20 25 30

25 His Val Ile Val Trp Leu Ser Gly Ala Gly Cys Thr Leu Ile Cys Glu
 35 40 45

30 Asp Asn Pro Phe Leu Leu Leu Phe Ser Gln Tyr Leu Gln Pro His His
 50 55 60

Pro Glu Ile Met Lys Pro Phe Ile Leu Gly His Lys Ser Ser Asn Gly
 65 70 75 80

35 Gly Leu Ser Pro Pro Ser Ala
 85

40 <210> 130
 <211> 64
 <212> PRT
 <213> Homo sapiens

45 <220>
 <221> SITE
 <222> (64)
 <223> Xaa equals stop translation

50 <400> 130
 Met Phe Tyr Met Val Cys Val Leu Gly Ser Gly Ala Gln Pro Leu Ser
 1 5 10 15

Glu Leu Ala Tyr Leu Ala Lys Leu Pro Thr Leu Gln Val Gly Lys Tyr
 20 25 30

55 Asn Pro Leu Phe Asn Lys Ala His Pro Leu His Pro Val Leu Thr Thr
 35 40 45

60 Phe Cys Glu Cys Ala Val Ile Phe Ser Cys Ser Ile Ala Arg Trp Xaa
 50 55 60

5

<210> 131
<211> 54
<212> PRT
<213> Homo sapiens

10

<400> 131
Met Arg Phe Gln Ser Tyr Leu Trp Pro Ser Arg Ile Leu Val Gly Thr
1 5 10 15

15

Tyr Cys Ile Ala Ala Glu Val Leu Phe Pro Ser Ala Leu Ala Ser Cys
20 25 30

Gly Pro Val Trp Gln Gly Gly Ala Pro Thr Lys Ser Trp Gln Pro Gly
35 40 45

20

Ala Lys Thr Ile Ile Pro
50

25

<210> 132
<211> 41
<212> PRT
<213> Homo sapiens

30

<220>
<221> SITE
<222> (41)
<223> Xaa equals stop translation

35

<400> 132
Met Arg Arg Trp Ala Gly Phe Gly Lys Ser Pro Gln Phe Trp Trp Thr
1 5 10 15

40

Gly Ile Leu Val Ala Leu Gly Ala Ala Leu Leu Gly Gly Pro Arg Leu
20 25 30

Gly Arg Arg Leu Thr Phe Gly Leu Xaa
35 40

45

<210> 133
<211> 69
<212> PRT
<213> Homo sapiens

50

<220>
<221> SITE
<222> (69)
<223> Xaa equals stop translation

55

<400> 133
Met Ala Leu Ala Ile Phe Ile Pro Val Leu Ile Ile Ser Leu Leu Leu
1 5 10 15

60

Gly Gly Ala Tyr Ile Tyr Ile Thr Arg Cys Arg Tyr Tyr Ser Asn Leu

20 25 30

Arg Leu Pro Leu Met Tyr Ser His Pro Tyr Ser Gln Ile Thr Val Glu
 35 40 45

5 Thr Glu Phe Asp Asn Pro Ile Tyr Glu Thr Gly Glu Thr Arg Glu Tyr
 50 55 60

10 Glu Val Ser Ile Xaa
 65

<210> 134

<211> 48

15 <212> PRT

<213> Homo sapiens

<220>

20 <221> SITE

<222> (48)

<223> Xaa equals stop translation

<400> 134

25 Met Gly Phe Leu Phe Leu His Ile Leu Pro Ser Ile Ile Asn Thr Arg
 1 5 10 15

Ser Ala Pro Gln Pro Thr Ser Cys Arg Met Gln Pro Glu Gln Gln Pro
 20 25 30

30 His Ser Thr Leu Lys Pro Val Ile Leu Gly Met Met Ile Ile Ser Xaa
 35 40 45

35

<210> 135

<211> 76

40 <212> PRT

<213> Homo sapiens

<400> 135

45 Met Ser Gly Leu Val Gly Gly Ser Arg Cys Ser Lys Val Arg Phe
 1 5 10 15

Arg Cys Phe Asn Gly Asp Ser Leu Leu Val Leu Val Leu Gln His His
 20 25 30

50 Phe Arg Leu Cys Ser Trp Cys Leu Ala Pro Ser Leu Phe Leu Leu
 35 40 45

Ser Cys Gln Val Val Ser Thr Met Met Glu Gln Asp Pro Val Ile Tyr
 50 55 60

55 Asp Asp Asp Asp Asp Leu Pro Asn Tyr Phe Ser Val
 65 70 75

60 <210> 136

<211> 55

<212> PRT
<213> Homo sapiens

5 <220>
 <221> SITE
 <222> (32)
 <223> Xaa equals any one of the naturally occurring L-amino acids

10 <220>
 <221> SITE
 <222> (39)
 <223> Xaa equals any one of the naturally occurring L-amino acids

15 <220>
 <221> SITE
 <222> (55)
 <223> Xaa equals stop translation

20 <400> 136
 Met Phe Leu Glu Leu Pro Met Gln His Ser Asp Val Leu Leu Phe Leu
 1 5 10 15
 Val Cys Trp Lys Ala Met Gly Ser Lys Lys Ser Pro Ser His Phe Xaa
 20 25 30
25 <400> 137
 Pro Glu Val Gly Gly Ile Xaa Pro Ser Phe Gly Met Leu Asn Val Thr
 35 40 45
 Leu Leu Arg Ser Leu Thr Xaa
 50 55

30 <210> 137
 <211> 54
35 <212> PRT
 <213> Homo sapiens

40 <400> 137
 Met Leu Val Leu Phe Pro Leu Leu Tyr Arg Gly Trp Ser Pro Val Pro
 1 5 10 15
 Gly Thr Ala Glu Gly Gly Met Cys Cys Cys Cys Leu Cys Ile Ser Arg
 20 25 30

45 <400> 138
 Tyr Ser Leu Leu Thr Ser Ser Gln Asp Lys Glu Pro Pro Tyr Glu Met
 35 40 45
 Ser Ser Ser Glu Leu Ser
 50

50 <210> 138
 <211> 36
55 <212> PRT
 <213> Homo sapiens

60 <220>
 <221> SITE
 <222> (33)
 <223> Xaa equals any one of the naturally occurring L-amino acids

5 <220>
 <221> SITE
 <222> (36)
 5 <223> Xaa equals stop translation

 10 <400> 138
 Met Thr Cys Tyr Glu Val Ile Leu Phe Phe Ile Lys Leu Phe Ser Asp
 1 5 10 15
 10 Met Gly Lys Tyr Lys Glu Cys Lys Glu Phe Lys Lys Gln Arg Thr Lys
 20 25 30

 15 Xaa Tyr Met Xaa
 35

 20 <210> 139
 <211> 80
 20 <212> PRT
 <213> Homo sapiens

 25 <400> 139
 Met Lys Ala Gln Pro Leu Glu Ala Leu Leu Leu Val Ala Leu Val Leu
 1 5 10 15

 25 Ser Phe Cys Gly Val Trp Phe Glu Asp Trp Leu Ser Lys Trp Arg Phe
 20 25 30

 30 Gln Cys Ile Phe Gln Leu Ala His Gln Pro Ala Leu Val Asn Ile Gln
 35 40 45

 35 Phe Arg Gly Thr Val Leu Gly Ser Glu Thr Phe Leu Gly Ala Glu Glu
 50 55 60

 35 Asn Ser Ala Asp Val Arg Ser Trp Gln Thr Leu Ser Tyr Phe Glu Leu
 65 70 75 80

 40

 45 <210> 140
 <211> 67
 45 <212> PRT
 <213> Homo sapiens

 45 <400> 140
 Met Ala Ala Ser Val Gly Arg Ala Thr Arg Ser Ala Ala Ala His Leu
 1 5 10 15

 50 Thr Gln Leu Pro Pro Ala Pro Arg Ala Gln Arg Thr Ser Pro Ala Gln
 20 25 30

 55 Pro Asp Glu Gly Lys Arg Arg Asp Ala Asp Pro Trp Arg Thr Gly Pro
 35 40 45

 60 Thr Val Asn Lys Thr Gly Ser Ile Pro Gly Arg Leu Arg Gly Trp Ala
 50 55 60

Arg Ala Glu
65

5 <210> 141
 <211> 51
 <212> PRT
 <213> Homo sapiens

10 <220>
 <221> SITE
 <222> (51)
 <223> Xaa equals stop translation

15 <400> 141
 Met Gly Trp Leu Cys Cys Glu Pro Ser Gly Leu Tyr Asn Leu Glu Lys
 1 5 10 15

20 Gln Tyr Phe Phe Phe Ser Ser Leu Gln Ala Gly Leu Pro Val Ile Val
 20 25 30

25 Ser Ser Gly Cys Thr Lys Ile Ala Tyr Gly Phe Ala Val Tyr Ser Pro
 35 40 45

30 Ser Ser Xaa
 50

35 <210> 142
 <211> 54
 <212> PRT
 <213> Homo sapiens

40 <400> 142
 Met Arg Arg Cys Val Arg His Val Leu Gly Ile Gly Leu Ile Val Leu
 1 5 10 15

45 Lys Asn Leu Tyr Phe His Lys Asn Ser Met Tyr Pro Ser Pro Lys Leu
 20 25 30

50 Ser Ser Phe Gln Glu Ala Phe Leu Phe Phe Leu Ile Leu Lys Asn
 35 40 45

55 Pro Leu Thr Leu Cys Ser
 50

60 <210> 143
 <211> 50
 <212> PRT
 <213> Homo sapiens

65 <220>
 <221> SITE
 <222> (50)
 <223> Xaa equals stop translation

70 <400> 143
 Ile His Pro Ser Arg Ser Thr Leu Ser Ser Gln Leu Val Thr Leu Pro
 1 5 10 15

Leu Phe Glu Leu Val Phe Pro Ile Pro Ser Ser Gln Ser Pro Phe Ser
 20 25 30

5 Leu Asn Tyr Leu Ser Glu Phe Pro Leu Pro Glu His Glu Pro Cys Leu
 35 40 45

Glu Xaa
 10 50

<210> 144
 <211> 87
 <212> PRT
 15 <213> Homo sapiens

<220>
 <221> SITE
 <222> (84)

20 <223> Xaa equals any one of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (87)

25 <223> Xaa equals stop translation

<400> 144
 Met Thr Cys Cys Cys Leu Leu Cys Lys Leu Gln Gly Ile Phe Phe Phe
 1 5 10 15

30 Ser Phe Asn Ser Ser Val Leu Lys Ser Ile Leu Gly Thr Thr Arg Thr
 20 25 30

Leu Ser Ala Pro Trp Ile Gly Val Ser Val Lys Gly Thr Gln Trp Ala
 35 35 40 45

Leu Gly Ser Ala Arg Pro Gly Cys Gly Ser Gln Leu Thr Ser Ser Leu
 50 55 60

40 Gly Gly Leu Arg Gln Val Ile Cys Gln Pro His Leu Gln Lys His Asp
 65 70 75 80

Ala Lys Leu Xaa Ser Val Xaa
 85

45 <210> 145
 <211> 57
 <212> PRT
 50 <213> Homo sapiens

<400> 145
 Met His Lys Cys Asn Thr Val Thr Arg Glu Leu Leu Gln Leu Ser Leu
 1 5 10 15

55 Leu Ile Leu Pro Ser Gln Cys Gly Asn Cys Ala Thr Ser Thr Lys Arg
 20 25 30

60 Gly Pro Arg Leu Leu Lys Tyr Phe Arg Thr Ser Pro Gln Glu Gln Thr
 35 40 45

Pro Leu His Leu Asp Ser Asp Cys Ser
 50 55

5 <210> 146
 <211> 87
 <212> PRT
 <213> Homo sapiens

10 <400> 146
 Met Ser His Cys Ala Arg Pro Leu Phe Phe Glu Thr Phe Phe Ile Leu
 1 5 10 15

15 Leu Ser Pro Arg Leu Lys Cys Ser Gly Thr Asn Thr Val His Tyr Ser
 20 25 30

Leu Asp Leu Leu Gly Ser Ser Asn Ser Ala Ser Val Pro Gln Val Gly
 35 40 45

20 Gly Leu Thr Asn Ala Gln His Asp Thr Trp Leu Ile Phe Val Phe Cys
 50 55 60

25 Val Cys Val Cys Glu Pro Leu Arg Arg Pro Trp Ala Ala Phe Leu Ile
 65 70 75 80

Ser Val Thr Ser Ser Ile Lys
 85

30 <210> 147
 <211> 230
 <212> PRT
 <213> Homo sapiens

35 <220>
 <221> SITE
 <222> (216)
 <223> Xaa equals any one of the naturally occurring L-amino acids

40 <400> 147
 Met Gly Leu Ala Leu Tyr Val Leu Pro Val Leu Gly Gln His Val Ala
 1 5 10 15

45 Thr Gln His Phe Pro Val Ala Glu Ala Glu Ala Val Val Leu Thr Leu
 20 25 30

Leu Ala Ile Tyr Ala Ala Gly Leu Ala Leu Pro His Asn Thr His Arg
 35 40 45

50 Val Val Ser Thr Gln Ala Pro Asp Arg Gly Trp Met Ala Leu Lys Leu
 50 55 60

55 Val Ala Leu Ile Tyr Leu Ala Leu Gln Leu Gly Cys Ile Ala Leu Thr
 65 70 75 80

Asn Phe Ser Leu Gly Phe Leu Leu Ala Thr Thr Met Val Pro Thr Ala
 85 90 95

60 Ala Leu Ala Lys Pro His Gly Pro Arg Thr Leu Tyr Ala Ala Leu Leu

	100	105	110	
	Val Leu Thr Ser Pro Ala Ala Thr Leu Leu Gly Ser Leu Phe Leu Trp			
5	115	120	125	
	Arg Glu Leu Gln Glu Ala Pro Leu Ser Leu Ala Glu Gly Trp Gln Leu			
	130	135	140	
10	Phe Leu Ala Ala Leu Ala Gln Gly Val Leu Glu His His Thr Thr Ala			
	145	150	155	160
	Pro Cys Ser Ser His Cys Cys Pro Trp Ala Ser Thr Pro Ala Gly Cys			
	165	170	175	
15	Phe Ser Gly Met Cys Ser Ser Gly Ser Glu Ile Cys Leu Ser Gly Leu			
	180	185	190	
	Gly Gln Arg Leu Pro Lys Asp Pro Ile Leu Pro Pro Ser Gly Glu Ile			
20	195	200	205	
	Asn Glu Cys Leu Phe Gln Gln Xaa Lys Lys Lys Lys Lys Lys Lys			
	210	215	220	
25	Lys Lys Lys Lys Gly Gly			
	225	230		
	<210> 148			
30	<211> 63			
	<212> PRT			
	<213> Homo sapiens			
	<220>			
35	<221> SITE			
	<222> (63)			
	<223> Xaa equals stop translation			
	<400> 148			
40	Gln Pro Ala Leu Leu Tyr Leu Val Pro Ala Cys Ile Gly Phe Pro Val			
	1	5	10	15
	Leu Val Ala Leu Ala Lys Gly Glu Val Thr Glu Met Phe Ser Tyr Glu			
	20	25	30	
45	Glu Ser Asn Pro Lys Asp Pro Ala Ala Val Thr Glu Ser Lys Glu Gly			
	35	40	45	
	Thr Glu Ala Ser Ala Ser Lys Gly Leu Glu Lys Lys Glu Lys Xaa			
50	50	55	60	
	<210> 149			
	<211> 18			
	<212> PRT			
55	<213> Homo sapiens			
	<220>			
	<221> SITE			
	<222> (18)			
60	<223> Xaa equals stop translation			

<400> 149
Gln Leu Ile Leu Ser Leu Leu Arg Gly Phe Cys Lys Thr Glu Arg Val
1 5 10 15
5 Gly Xaa

10 <210> 150
<211> 16
<212> PRT
<213> Homo sapiens

15 <220>
<221> SITE
<222> (16)
<223> Xaa equals stop translation

20 <400> 150
Met Ala Leu Gly Ala Arg Glu Leu Pro Gly Ser Leu Ser Arg Trp Xaa
1 5 10 15
25

30 <210> 151
<211> 22
<212> PRT
<213> Homo sapiens

35 <220>
<221> SITE
<222> (22)
<223> Xaa equals stop translation

40 <400> 151
Met Tyr Ser Phe Ser Val Leu Glu Ile Thr Cys Phe Ile Leu Phe Leu
1 5 10 15
Trp Pro Ser Trp Val Xaa
20

45 <210> 152
<211> 25
<212> PRT
<213> Homo sapiens

50 <220>
<221> SITE
<222> (25)
<223> Xaa equals stop translation

55 <400> 152
Met Lys Ile Lys Gln Arg Phe Ser Leu Leu Phe His Cys Pro Phe
1 5 10 15
60 Pro Pro Cys Cys Leu Ser Leu Gly Xaa

20 25

5 <210> 153
 <211> 40
 <212> PRT
 <213> Homo sapiens

10 <400> 153
 Met Asn Gly Leu Phe Gln Leu Glu Ile Ser His Lys Leu Trp Thr Lys
 1 5 10 15
 Ser Lys Thr Ser Leu Met Thr Leu Leu Ser Val Met Ala Leu Leu Trp
 20 25 30
 15 Lys Ile Leu Trp Ser Arg Ala Ile
 35 40

20 <210> 154
 <211> 25
 <212> PRT
 <213> Homo sapiens

25 <220>
 <221> SITE
 <222> (25)
 <223> Xaa equals stop translation

30 <400> 154
 Met Thr Pro Gly Leu Phe Leu Tyr Phe Val Cys Val Cys Val Ser His
 1 5 10 15
 Cys Ala Gly Leu Gly Gln Leu Ser Xaa
 20 25

35 <210> 155
 <211> 103
 40 <212> PRT
 <213> Homo sapiens

40 <400> 155
 Ile Arg His Glu Leu Gly Cys Ser Trp Arg Phe Arg Ala Val Lys Ala
 1 5 10 15
 Ala Ser Ala Gln Gly Leu Phe Leu Ser Ala Pro Gly Pro Ala Ala Arg
 20 25 30

45 <400> 155
 Arg Cys His Gly Val Val Arg Cys Phe Ser Thr Cys Arg Ala Leu Thr
 35 40 45
 Ala Arg Cys Thr Gly Arg Val Pro Trp Glu Ala Cys Leu Tyr Ser Ser
 50 55 60

50 <400> 155
 Glu Pro Pro Leu Thr Glu Thr Val Ala Arg Ser Val Ser Trp Thr Cys
 65 70 75 80

55 <400> 155
 Glu Leu Ala Leu Thr Cys Tyr Ala Pro Arg Ala Leu Ser Gly Ala Pro
 85 90 95

Val Leu Cys Arg His Asp Val
 100

5 <210> 156
 <211> 46
 <212> PRT
 <213> Homo sapiens

10 <400> 156
 Phe Leu Ala Ile His Phe Pro Thr Asp Phe Pro Leu Lys Pro Pro Lys
 1 5 10 15

15 Val Ala Phe Thr Arg Met Tyr Phe Pro Asn Ser Asn Ser Asn Gly Ser
 20 20 25 30

20 Thr Cys Leu Asp Ile Leu Trp Ser Gln Trp Ser Pro Ala Leu
 35 35 40 45

25 <210> 157
 <211> 101
 <212> PRT
 <213> Homo sapiens

30 <400> 157
 Met Leu Leu Thr Pro His Phe Asn Val Ala Asn Pro Gln Asn Leu Leu
 1 5 10 15

35 Ala Gly Leu Trp Leu Glu Asn Glu His Ser Phe Thr Leu Met Ala Pro
 35 20 25 30

40 Glu Arg Ala Arg Thr His His Cys Gln Pro Glu Glu Arg Lys Val Leu
 35 35 40 45

45 Phe Cys Leu Phe Pro Ile Val Pro Asn Ser Gln Ala Gln Val Gln Pro
 50 50 55 60

50 Pro Gln Met Pro Pro Phe Cys Cys Ala Ala Ala Lys Glu Lys Thr Gln
 65 70 75 80

55 Glu Glu Gln Leu Gln Glu Pro Leu Gly Ser Gln Cys Pro Asp Thr Cys
 85 90 95

60 45 Pro Asn Ser Leu Cys
 100

50 <210> 158
 <211> 211
 <212> PRT
 <213> Homo sapiens

55 <400> 158
 Met Arg Leu Phe Leu Trp Asn Ala Val Leu Thr Leu Phe Val Thr Ser
 1 5 10 15

60 Leu Ile Gly Ala Leu Ile Pro Glu Pro Glu Val Lys Ile Glu Val Leu
 20 25 30

Gln Lys Pro Phe Ile Cys His Arg Lys Thr Lys Gly Gly Asp Leu Met
 35 40 45

5 Leu Val His Tyr Glu Gly Tyr Leu Glu Lys Asp Gly Ser Leu Phe His
 50 55 60

10 Ser Thr His Lys His Asn Asn Gly Gln Pro Ile Trp Phe Thr Leu Gly
 65 70 75 80

15 Ile Leu Glu Ala Leu Lys Gly Trp Asp Gln Gly Leu Lys Gly Met Cys
 85 90 95

20 Val Gly Glu Lys Arg Lys Leu Ile Ile Pro Pro Ala Leu Gly Tyr Gly
 100 105 110

25 Lys Glu Gly Lys Gly Lys Ile Pro Pro Glu Ser Thr Leu Ile Phe Asn
 115 120 125

30 Ile Asp Leu Leu Glu Ile Arg Asn Gly Pro Arg Ser His Glu Ser Phe
 130 135 140

35 Gln Glu Met Asp Leu Asn Asp Asp Trp Lys Leu Ser Lys Asp Glu Val
 145 150 155 160

40 Lys Ala Tyr Leu Lys Lys Glu Phe Glu Lys His Gly Ala Val Val Asn
 165 170 175

45 Glu Ser His His Asp Ala Leu Val Glu Asp Ile Phe Asp Lys Glu Asp
 180 185 190

50 Glu Asp Lys Asp Gly Phe Ile Ser Ala Arg Glu Phe Thr Tyr Lys His
 195 200 205

55 Asp Glu Leu
 210

60 <210> 159
 40 <211> 186
 <212> PRT
 <213> Homo sapiens

65 <400> 159
 45 Glu Val Lys Ile Glu Val Leu Gln Lys Pro Phe Ile Cys His Arg Lys
 1 5 10 15

50 Thr Lys Gly Gly Asp Leu Met Leu Val His Tyr Glu Gly Tyr Leu Glu
 20 25 30

55 Lys Asp Gly Ser Leu Phe His Ser Thr His Lys His Asn Asn Gly Gln
 35 40 45

60 Pro Ile Trp Phe Thr Leu Gly Ile Leu Glu Ala Leu Lys Gly Trp Asp
 50 55 60

65 Gln Gly Leu Lys Gly Met Cys Val Gly Glu Lys Arg Lys Leu Ile Ile
 65 70 75 80

70 Pro Pro Ala Leu Gly Tyr Gly Lys Glu Gly Lys Gly Ile Pro Pro

	85	90	95	
	Glu Ser Thr Leu Ile Phe Asn Ile Asp Leu Leu Glu Ile Arg Asn Gly			
	100	105	110	
5	Pro Arg Ser His Glu Ser Phe Gln Glu Met Asp Leu Asn Asp Asp Trp			
	115	120	125	
10	Lys Leu Ser Lys Asp Glu Val Lys Ala Tyr Leu Lys Lys Glu Phe Glu			
	130	135	140	
	Lys His Gly Ala Val Val Asn Glu Ser His His Asp Ala Leu Val Glu			
	145	150	155	160
15	Asp Ile Phe Asp Lys Glu Asp Glu Asp Lys Asp Gly Phe Ile Ser Ala			
	165	170	175	
	Arg Glu Phe Thr Tyr Lys His Asp Glu Leu			
20	180	185		
	<210> 160			
	<211> 633			
	<212> DNA			
25	<213> Homo sapiens			
	<400> 160			
	ATGAGGCTTT TCTTGTGGAA CGCGGTCTTG ACTCTGTTCG TCACCTCTTT GATTGGGCT		60	
30	TTGATCCCTG AACCAGAAGT GAAAATTGAA GTTCTCCAGA AGCCATTCACT CTGCCATCGC		120	
	AAGACCAAAG GAGGGGATTG GATGTTGGTC CACTATGAAG GCTACTTAGA AAAGGACGGC		180	
	TCCCTATTTC ACTCCACTCA CAAACATAAC AATGGTCAGC CCATTTGGTT TACCTGGGC		240	
35	ATCCTGGAGG CTCTCAAAGG TTGGGACCAAG GGCTTGAAAG GAATGTGTGT AGGAGAGAAG		300	
	AGAAAGCTCA TCATTCCCTCC TGCTCTGGGC TATGGAAAAG AAGGAAAAGG TAAAATTCCC		360	
40	CCAGAAAGTA CACTGATATT TAATATTGAT CTCCTGGAGA TTCGAAATGG ACCAAGATCC		420	
	CATGAATCAT TCCAAGAAAT GGATCTTAAT GATGACTGGA AACTCTCTAA AGATGAGGTT		480	
	AAAGCATATT TAAAGAAGGA GTTTGAAAAA CATGGTGCGG TGGTGAATGA AAGTCATCAT		540	
45	GATGCTTTGG TGGAGGATAT TTTTGATAAA GAAGATGAAG ACAAAAGATGG GTTTATATCT		600	
	GCCAGAGAAT TTACATATAA ACACGATGAG TTA		633	
50	<210> 161			
	<211> 22			
	<212> PRT			
55	<213> Homo sapiens			
	<400> 161			
	Leu Arg Ser Val Val Gln Asp His Pro Gly Gln His Gly Glu Thr Pro			
	1	5	10	15
60				

Ser Leu Leu Lys Ile Gln
20

5 <210> 162
 <211> 57
 <212> PRT
 <213> Homo sapiens

10 <220>
 <221> SITE
 <222> (34)
 <223> Xaa equals any one of the naturally occurring L-amino acids

15 <400> 162
 Met Phe Tyr Asn Phe Val Arg Gln Leu Asp Thr Val Ser Ile Glu His
 1 5 10 15

20 Ala Gly Lys Ser Lys Leu Lys Met Thr Val Gly Thr Lys Leu Thr Ser
 20 25 30

 Gly Xaa Gly Pro Arg Lys Ser Ser Gln Ser Gly Arg Ile Ala Ala Ser
 35 40 45

25 Ile Thr Asp Cys Gln Gln Cys Lys Ala
 50 55

30 <210> 163
 <211> 46
 <212> PRT
 <213> Homo sapiens

35 <220>
 <221> SITE
 <222> (16)
 <223> Xaa equals any one of the naturally occurring L-amino acids

40 <400> 163
 Met Glu Ala Ala Ile Leu Pro Leu Trp Leu Leu Phe Leu Gly Pro Xaa
 1 5 10 15

 Pro Glu Val Ser Phe Val Pro Thr Val Ile Phe Asn Leu Asp Phe Pro
 20 25 30

45 Ala Cys Ser Ile Leu Thr Val Ser Ser Cys Leu Thr Lys Leu
 35 40 45

50 <210> 164
 <211> 25
 <212> PRT
 <213> Homo sapiens

55 <400> 164
 Asn His Gly His Ser Cys Phe Leu Cys Glu Ile Val Ile Arg Ser Gln
 1 5 10 15

60 Phe His Thr Thr Tyr Glu Pro Glu Ala
 20 25

5 <210> 165
 <211> 48
 <212> PRT
 <213> Homo sapiens

10 <400> 165
 Ser Gly Arg His Arg Val Glu Leu Gln Leu Leu Phe Pro Leu Val Arg
 1 5 10 15

Val Asn Phe Glu Leu Gly Val Asn His Gly His Ser Cys Phe Leu Cys
 20 25 30

15 Glu Ile Val Ile Arg Ser Gln Phe His Thr Thr Tyr Glu Pro Glu Ala
 35 40 45

20

25 <210> 166
 <211> 141
 <212> PRT
 <213> Homo sapiens

30 <400> 166
 Met Asn Ala Arg Gly Leu Gly Ser Glu Leu Lys Asp Ser Ile Pro Val
 1 5 10 15

Thr Glu Leu Ser Ala Ser Gly Pro Phe Glu Ser His Asp Leu Leu Arg
 20 25 30

35 Lys Gly Phe Ser Cys Val Lys Asn Glu Leu Leu Pro Ser His Pro Leu
 35 40 45

40 Glu Leu Ser Glu Lys Asn Phe Gln Leu Asn Gln Asp Lys Met Asn Phe
 50 55 60

45 Ser Thr Leu Arg Asn Ile Gln Gly Leu Phe Ala Pro Leu Lys Leu Gln
 65 70 75 80

Met Glu Phe Lys Ala Val Gln Gln Val Gln Arg Leu Pro Phe Leu Ser
 85 90 95

50 Ser Ser Asn Leu Ser Leu Asp Val Leu Arg Gly Asn Asp Glu Thr Ile
 100 105 110

55 Gly Phe Glu Asp Ile Leu Asn Asp Pro Ser Gln Ser Glu Val Met Gly
 115 120 125

Glu Pro His Leu Met Val Glu Tyr Lys Leu Gly Leu Leu
 130 135 140

60

<210> 167
 <211> 15
 <212> PRT
 <213> Homo sapiens

<400> 167
 Gly Gly Asn Lys Tyr Gln Thr Ile Asp Asn Tyr Gln Pro Tyr Pro
 1 5 10 15

5 <210> 168
 <211> 20
 <212> PRT
 <213> Homo sapiens

10 <400> 168
 Pro Leu Leu Gly Val Ser Ala Thr Leu Asn Ser Val Leu Asn Ser Asn
 1 5 10 15

15 Ala Ile Lys Asn
 20

20 <210> 169
 <211> 14
 <212> PRT
 <213> Homo sapiens

25 <400> 169
 Gly Ser Ala Val Ser Ala Ala Pro Gly Ile Leu Tyr Pro Gly
 1 5 10

30 <210> 170
 <211> 81
 <212> PRT
 <213> Homo sapiens

35 <400> 170
 Ala Gly Ile Gln His Glu Leu Ala Cys Asp Asn Pro Gly Leu Pro Glu
 1 5 10 15

40 Asn Gly Tyr Gln Ile Leu Tyr Lys Arg Leu Tyr Leu Pro Gly Glu Ser
 20 25 30

45 Leu Thr Phe Met Cys Tyr Glu Gly Phe Glu Leu Met Gly Glu Val Thr
 35 40 45

Ile Arg Cys Ile Leu Gly Gln Pro Ser His Trp Asn Gly Pro Leu Pro
 50 55 60

55 Val Cys Lys Val Ala Glu Ala Ala Glu Thr Ser Leu Glu Gly Gly
 65 70 75 80

60 Asn

55 <210> 171
 <211> 27
 <212> PRT
 <213> Homo sapiens

60 <400> 171
 Gln Pro Ser His Trp Asn Gly Pro Leu Pro Val Cys Lys Val Ala Glu

1	5	10	15
Ala Ala Ala Glu Thr Ser Leu Glu Gly Gly Asn			
	20	25	
5			
<210> 172			
<211> 13			
<212> PRT			
10	<213> Homo sapiens		
<400> 172			
Tyr Glu Thr Gly Glu Thr Arg Glu Tyr Glu Val Ser Ile			
	1	5	10
15			
<210> 173			
<211> 195			
<212> PRT			
20	<213> Homo sapiens		
<220>			
<221> SITE			
<222> (40)			
25	<223> Xaa equals any one of the naturally occurring L-amino acids		
<220>			
<221> SITE			
<222> (161)			
30	<223> Xaa equals any one of the naturally occurring L-amino acids		
<400> 173			
Asp Asp Asp Gly Leu Pro Phe Pro Thr Asp Val Ile Gln His Arg Leu			
	1	5	10
35			15
Arg Gln Ile Glu Ala Gly Tyr Lys Gln Glu Val Glu Gln Leu Arg Arg			
	20	25	30
Gln Val Arg Asp Ser Asp Glu Xaa Gly His Pro Ser Leu Leu Cys Pro			
40	35	40	45
Ser Ser Arg Ala Pro Met Asp Tyr Glu Asp Asp Phe Thr Cys Leu Lys			
	50	55	60
45	Glu Ser Asp Gly Ser Asp Thr Glu Asp Phe Gly Ser Asp His Ser Glu		
	65	70	75
			80
Asp Cys Leu Ser Glu Ala Ser Trp Glu Pro Val Asp Lys Lys Glu Thr			
	85	90	95
50	Glu Val Thr Arg Trp Val Pro Asp His Met Ala Ser His Cys Tyr Asn		
	100	105	110
55	Cys Asp Cys Glu Phe Trp Leu Ala Lys Arg Arg His His Cys Arg Asn		
	115	120	125
Cys Gly Asn Val Phe Cys Ala Gly Cys Cys His Leu Lys Leu Pro Ile			
	130	135	140
60	Pro Asp Gln Gln Leu Tyr Asp Pro Val Leu Val Cys Asn Ser Cys Tyr		

	145	150	155	160
	Xaa Thr His Ser Ser Leu Ser Cys Gln Gly Thr His Glu Pro Thr Ala			
5	165	170	175	
	Glu Glu Thr His Cys Tyr Ser Phe Gln Leu Asn Ala Gly Glu Lys Pro			
	180	185	190	
10	Val Gln Phe			
	195			
	<210> 174			
	<211> 28			
15	<212> PRT			
	<213> Homo sapiens			
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	Arg Trp Val Pro Asp His Met Ala Ser His Cys Tyr			
	20	25		
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	<211> 10			
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30	<213> Homo sapiens			
	<400> 175			
	His His Cys Arg Asn Cys Gly Asn Val Phe			
	1	5	10	
35				
	<210> 176			
	<211> 14			
	<212> PRT			
40	<213> Homo sapiens			
	<400> 176			
	Arg Leu Arg Gln Ile Glu Ala Gly Tyr Lys Gln Glu Val Glu			
	1	5	10	
45				
	<210> 177			
	<211> 87			
	<212> PRT			
50	<213> Homo sapiens			
	<400> 177			
	Met Ser His Cys Ala Arg Pro Leu Phe Phe Glu Thr Phe Ile Leu			
	1	5	10	15
55	Leu Ser Pro Arg Leu Lys Cys Ser Gly Thr Asn Thr Val His Tyr Ser			
	20	25	30	
	Leu Asp Leu Leu Gly Ser Ser Asn Ser Ala Ser Val Pro Gln Val Gly			
60	35	40	45	

Gly Leu Thr Asn Ala Gln His Asp Thr Trp Leu Ile Phe Val Phe Cys
50 55 60

5 Val Cys Val Cys Glu Pro Leu Arg Arg Pro Trp Ala Ala Phe Leu Ile
65 70 75 80

Ser Val Thr Ser Ser Ile Lys
85

10 <210> 178
<211> 30
<212> PRT
<213> Homo sapiens

15 <400> 178
Val Pro Gln Val Gly Gly Leu Thr Asn Ala Gln His Asp Thr Trp Leu
1 5 10 15

20 Ile Phe Val Phe Cys Val Cys Glu Pro Leu Arg Arg
- 20 25 30

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/14613

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 436/501; 435/320.1, 69.1, 6, 252.3; 530/350, 24, 387.1; 536/23.1, 23.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CROSS et al. Purification of CpG islands using a methylated DNA binding column. Nature Genetics. March 1994, Vol. 6, No. 3, 236-244, see entire document and attached sequence.	1 and 8-10

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance		
E earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
O document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

25 SEPTEMBER 1998

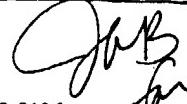
Date of mailing of the international search report

21 OCT 1998

Name and mailing address of the ISA/US
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/14613

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C12N 15/11, 15/63, 15/00, 15/12; A61K 38/17; C07K 16/00; C12P 21/02; C12Q 1/68; G01N 33/68

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

436/501; 435/320.1, 69.1, 6, 252.3; 530/350, 24, 387.1; 536/23.1, 23.5

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN, MPSRCH (SEQ ID NOs 11 and 83 only). One nucleotide sequence and one amino acid sequence have been searched. It is not clear which sequences are embraced by the claims because the claims refer to sequences X and Y. The table at pages 79 to 84 contains many sequences X and Y, yet the claims refer to X and Y in the singular only. If the claims are to embrace more than one X and more than one Y, it is not clear whether each X sequence always requires the corresponding sequence X (e.g., see claim 1(c)). Additionally, the claims are in improper form in referring to the description (see PCT Rule 6.2(a)). Accordingly, the first X nucleotide sequence disclosed and the first Y amino acid sequence disclosed were searched.

